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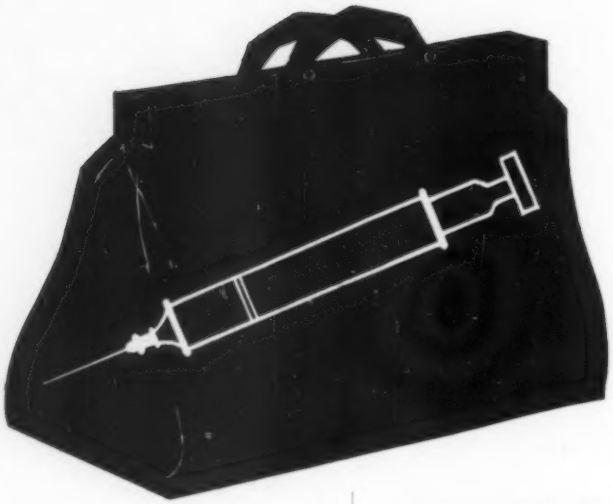

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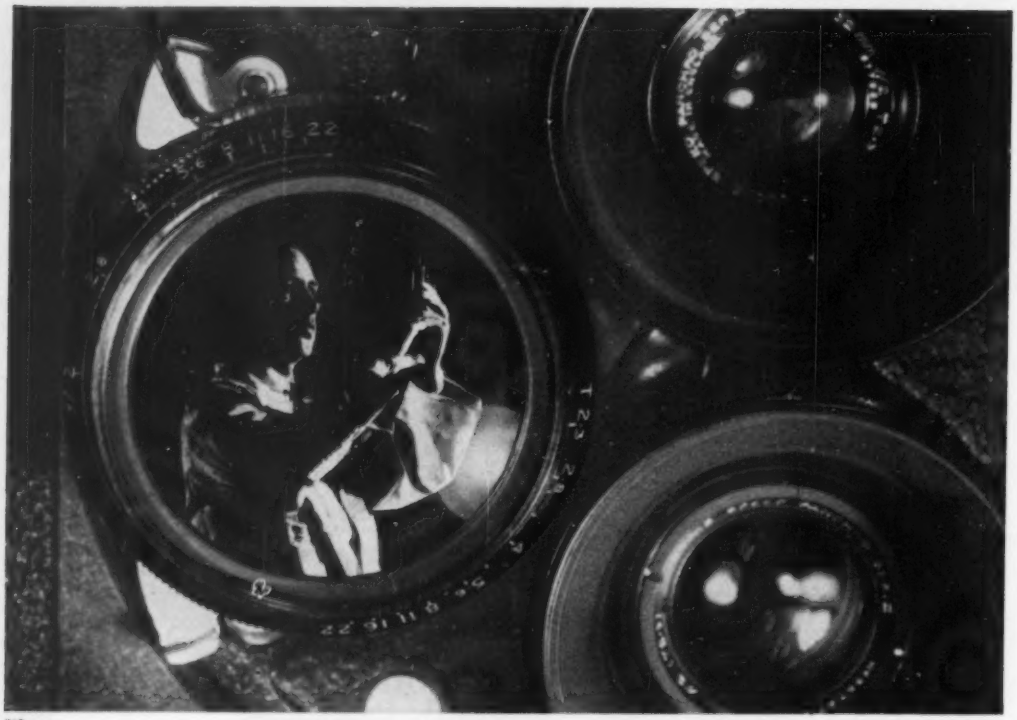

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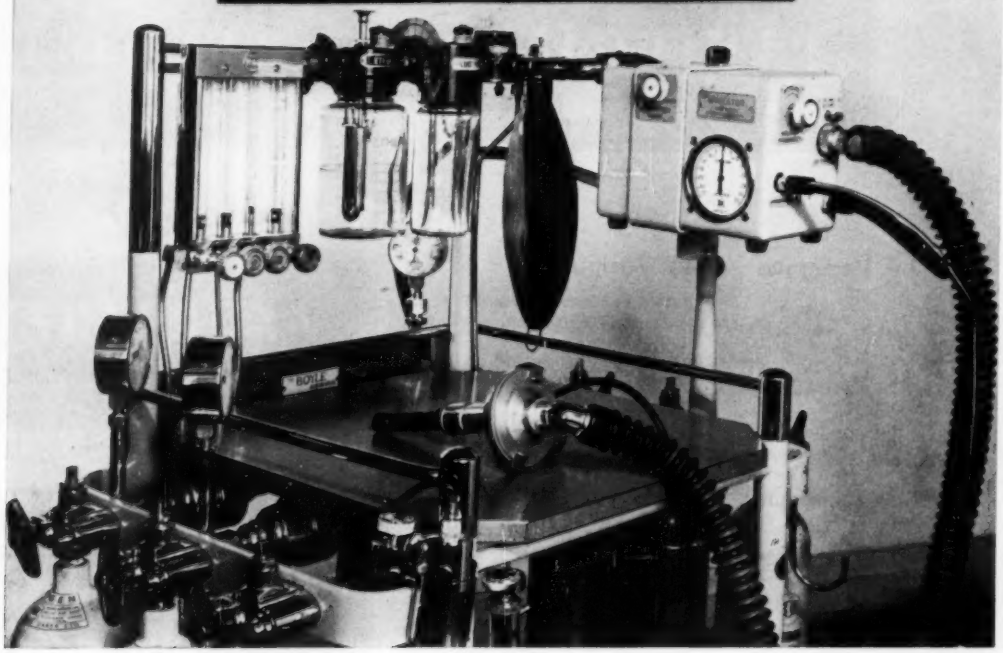

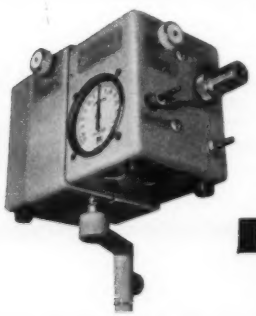

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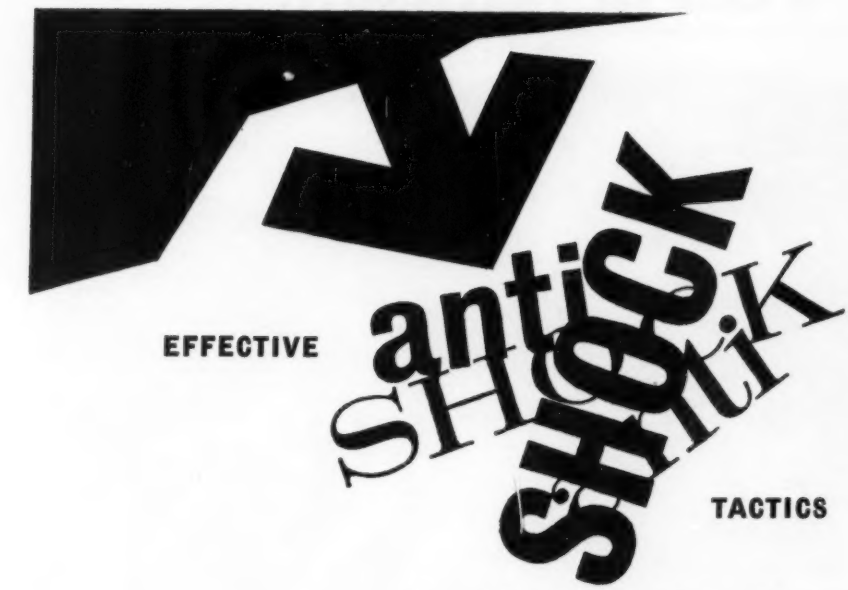

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXIII, No. 9 SEPTEMBER 1961

EDITORIAL

A BRAZILIAN HONOURED

AN interesting award that will gratify many of his friends in this country has been that of Commander of the British Empire to Professor Mario D'Almeida of Rio de Janeiro. Professor D'Almeida holds the only chair of Anaesthesia in South America and was the first South American to be elected to the F.F.A.R.C.S. He did his post-graduate anaesthetic work in the Department of Anaesthetics at the London Hospital and in Oxford, and has been at the Strangers Hospital in Rio de Janeiro for over 30 years. During the war years and since he has done valuable work for the British Community in Rio and has played a leading part in encouraging visits by prominent British Surgeons and Anaesthetists to Brazil.

PUBLISHERS' NOTE

READERS of the *British Journal of Anaesthesia* will without doubt be interested to learn of the recent award of Honorary Fellowships to both General Editors of this Journal. To Dr. E. Falkner Hill in the Faculty of Anaesthetists of the Royal College of Surgeons of England and to Professor Cecil Gray in the Faculty of Anaesthetists of the Royal Australasian College of Surgeons. Dr. Falkner Hill's Fellowship was conferred by the Dean of the Faculty at the Board of Faculty meeting on Wednesday, March 15, and Professor Gray's during his tour of Australasia as Sims Travelling Commonwealth Professor, at the meeting of the Royal Australasian College of Surgeons held in Brisbane.

Dr. Falkner Hill is also nominated to receive the Honorary Fellowship of the Association of Anaesthetists of Great Britain and Ireland at the Annual Meeting to be held in Dublin in October.

Brit. J. Anaesth. (1961), **33**, 422

ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA

VII: THE EFFECTS OF NINE PHENOTHIAZINE DERIVATIVES

BY

JAMES MOORE AND JOHN W. DUNDEE
Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

IN the original publication on chlorpromazine, Courvoisier and her associates (1953) reported that this phenothiazine potentiated the intensity and duration of action of analgesic drugs in animals. They did not, however, show that chlorpromazine itself possessed any analgesic action. Schneider (1954) also found that it increased the duration of morphine analgesia in mice. Kopera and Armitage (1954), on the other hand, were unable to demonstrate any potentiation of morphine analgesia by either chlorpromazine or promethazine. All these workers used the same species of animals in their studies, employed the same technique for the measurement of analgesia and injected the same dosage of chlorpromazine (10 mg/kg). More recently, Tripod and Gross (1957), using a similar experimental technique, found that chlorpromazine increased the duration of morphine-induced analgesia, and demonstrated that promazine had a similar action.

Despite the widely publicized claims for the potentiation of analgesic action by phenothiazines, the authors were unable to find reports of any other animal experiments which have a direct bearing on the subject. Controlled observations in man are also very few. Using the Hardy, Wolff and Goodell (1948) technique for measuring pain, Hougs and Skouby (1957) found that the chlorinated phenothiazines possessed an analgesic action which was not present in the nonchlorinated compounds. The most extensive study has been that of Boreus and Sandberg (1959) who also used the thermal method for measuring analgesia and carried out investigations in 184 subjects aged between 20 and 25 years. They found that 15 mg of chlorpromazine had some analgesic action and that it augmented the analgesic effect of methadone 6 mg. No analgesic activity could be demonstrated for pecazine 15 mg and when combined with methadone it antagonized the analgesic action of the latter. Acetylpromazine was studied in 5-mg doses and was found to have no analgesic effect but it did not antagonize the action of methadone.

Judging by the amount of data in the literature, the unsubstantiated claims made for the phenothiazines may be based on observations of the amount of analgesic drugs required in the postoperative period in patients to whom the drugs have already been given either in pre-anaesthetic medication or during anaesthesia. In 1950, Laborit, who popularized the use of these drugs, found that postoperative analgesic drugs were not required when diethazine and promethazine had been given before and after operation. This was attributed to the "central analgesic and hypnotic" properties of these drugs.

Dripps et al. (1955) reported that the addition of 5 to 12 mg of chlorpromazine to the usual premedication increased its efficacy and augmented the anaesthetic action of nitrous oxide and oxygen mixtures. The use of several oral doses of 25 mg of chlorpromazine before and after anaesthesia was studied in patients undergoing thoracic surgery by Boulton (1955). He found that this drug made patients indifferent to pain, reducing the postoperative requirements of pethidine by 23 per cent in females and by 6 to 7 per cent in males. He concluded that chlorpromazine potentiated the action of analgesic drugs. In a well organized trial, in which variables were reduced to minimum, Dryberg and Johannsen (1958) could find no difference in the requirements of analgesic drugs in the postoperative period between patients premedicated with morphine 10 mg or chlorpromazine 50 mg. The results of these clinical studies

suggest that chlorpromazine may have some analgesic action of its own and that it increases the efficacy of analgesic drugs.

Sadove (1956) reported that a combination of promethazine and an analgesic drug gave the same degree of relief from pain as was obtained using a larger dose of analgesic alone. The pre- and postanaesthetic use of promethazine reduced the requirements of analgesics to one-sixth to one-half of normal. Watrous (1957), although finding that promethazine was an unsatisfactory sedative drug for premedication, noted that it decreased the dose of thiopentone and of analgesic drugs required during anaesthesia. He gave no figures to support his claim. Contrary to the above findings, Bergner and Ma (1960) did not find evidence of any analgesia in 271 patients premedicated with promethazine and noted that both the frequency and intensity of their reactions to stimuli were similar to those of patients who had been given a barbiturate. Similarly, Pitcher (1959) found that the intravenous use of promethazine during anaesthesia did not "settle" patients in a manner which would be expected from the opiates.

In his technique of "ataralgesia", in which he attempted to produce total analgesia without loss of consciousness, Hayward-Butt (1957) combined pethidine, pecazine and amiphenazole and attributed his success to the potentiating effect of pecazine on pethidine. However, Boreus and Sandberg (1959), as already mentioned, demonstrated an anti-analgesic effect of pecazine but found that amiphenazole potentiated the analgesic action of methadone. These results suggest an alternative explanation for the good results reported by Hayward-Butt (1957), which is supported by the findings of Davies (1959). When trying to evolve a suitable technique of analgesia for dressing of burns, she found that pethidine with amiphenazole was superior to a mixture of pethidine, amiphenazole and pecazine.

Despite the number of publications which deal with the effects of promethazine and pecazine, there is much less concrete evidence in support of their having an analgesic action, or a potentiating effect on analgesic drugs, than there is for chlorpromazine. None of the newer phenothiazine derivatives appears to have been studied in any detail and it has been possible to find references to the use of perphenazine and triflupromazine only. Phillips et al. (1958) in two comparable groups of patients found that the addition of 5 mg of perphenazine to the standard premedication reduced the incidence of requirements of analgesic drugs in the postoperative period from 20 per cent to 9.2 per cent. Lear and his colleagues (1959), also in a carefully controlled trial, found that triflupromazine 10 to 20 mg halved the requirements of postoperative analgesic drugs.

Space does not permit a detailed discussion of the findings relating to the use of phenothiazine derivatives in chronic pain or in obstetrics. Furthermore, it is difficult to be certain whether any beneficial effect which they may have under these circumstances is indicative of a true analgesic action or is due to a potentiation of analgesic drugs. It must be remembered that an ataractic action, with decrease in anxiety reactions, can be produced in experimental animals with doses of chlorpromazine and morphine which are insufficient to cause a detectable degree of analgesia (Ambrus et al., 1957). It is worthy of note that the drug which has proved most beneficial as an adjuvant in the management of chronic pain is chlorpromazine (Sadove et al., 1954; Dundee, 1957). In the field of obstetrics beneficial effects have been reported following the use of chlorpromazine (Browne and Mannion, 1955; Karp, Lamb and Benaron, 1955; Savage, 1955), promethazine (Hobbs and Carroll, 1958; Adelman et al., 1959; O'Sullivan, 1960), promazine (Macvicar and Murray, 1960), and perphenazine (Harer, 1958).

When investigating the reliability of a method of analgesimetry the present authors found that a mixture of pethidine 100 mg and promethazine 50 mg (Pamergan P.100) was almost devoid of analgesic activity, whereas by the same technique they consistently demonstrated an analgesic action following the administration of pethidine alone. This led to an investigation of the action of promethazine on the patients' appreciation of pain which has been reported recently (Moore and Dundee, 1961a). Irrespective of the route of administration, it was found that 50 mg of promethazine was followed by an increased sensitivity to pain and that it consistently antagonized the analgesia produced by pethidine. These findings prompted a study of the action of a smaller (10 mg) dose of promethazine and also of other phenothiazine derivatives used in anaesthetic

practice. This report describes the results of this investigation and attempts to relate their actions to the chemical structure of the drugs. It will be apparent from the preliminary discussion that similar comparative data on this action of the phenothiazine derivatives is not available in the literature.

Phenothiazine derivatives studied.

The chemical structure of these is shown in figure 1, in which the drugs have been grouped according to the classification described by Rees (1960). Some difficulty was encountered in deciding upon equipotent doses of different phenothiazine derivatives and eventually is was decided to use the dosage of each drug most commonly employed in anaesthetic practice. Since different publications have described the use of phenothiazine derivatives in anaesthesia for a variety of purposes (pre-operative sedation, antisialogogue effect, production of hypothermia, potentiation of anaesthetics and anti-emetic action) it is not

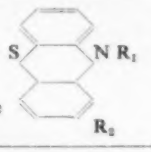
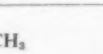
Generic name	Proprietary name	 Phenothiazine nucleus
Dimethyl amino propyl side chain		
1. Chlorpromazine	Largactil	R_1 $CH_2\,CH_2\,CH_2\,N(CH_3)_2$ HCl R_2 Cl
2. Promethazine	Phenergan	R_1 $CH_2\,CH(CH_3)\,N(CH_3)_2$ HCl R_2 H
3. Promazine	Sparine	R_1 $CH_2\,CH_2\,CH_2\,N(CH_3)_2$ HCl R_2 H
4. Trifluopromazine	Vespral	R_1 $CH_2\,CH_2\,CH_2\,N(CH_3)_2$ HCl R_2 CF_3
5. Trimeprazine	Vallergan	R_1 $CH_2\,CH(CH_3)\,CH_2\,N(CH_3)_2$ R_2 H
Piperazine side chain		
1. Prochlorperazine	Stemetil	R_1 $CH_2\,CH_2\,CH_2\,N$ $N\,CH_3$ R_2 Cl
2. Perphenazine	Fentazin	R_1 $CH_2\,CH_2\,CH_2\,N$ $N\,CH_2\,CH_2\,OH$ R_2 Cl
3. Trifluoperazine	Stelazine	R_1 $CH_2\,CH_2\,CH_2\,N$ $N\,CH_3$ 2 HCl R_2 CF_3
Piperidine side chain		
1. Pecazine	Pacatal	R_1 CH_2  $N\,CH_3$ R_2 H

FIG. 1
Chemical structure of phenothiazine derivatives studied.

certain that the dosages of the different drugs used in this study are strictly comparable as regards any single one of their various facets of action.

METHOD

The patient's appreciation of pain was estimated by the method of analgesimetry described by Dundee and Moore (1960). This consists of the gradual application of pressure to the anterior surface of the tibia. Two endpoints were determined (*a*) when the feeling of pressure changed to pain (threshold) and (*b*) when the pain became unbearable or when the limb was moved in response to the stimulus (response). Previous tests have determined the degree of error associated with this method and have demonstrated its reliability on repeated usage.

RESULTS

Intravenous injection.

This would seem to be the most suitable route of administration for this study but unfortunately in the doses used the phenothiazine derivatives caused an appreciable degree of hypotension. Apart from the difficulties in reversing the falls in blood pressure and their frequent persistence during the course of the subsequent anaesthesia, it was found repeatedly that the scatter of duplicate readings became more marked during profound hypotension and thus the significance of the findings became less. In addition to this, the intravenous injection of most of the phenothiazine derivatives caused a marked degree of restlessness and agitation in the conscious subject. This phenomenon occurred within 10 minutes of injection and frequently persisted for 15 to 20 minutes. The restlessness was so severe in some patients that it was necessary to abandon the study and induce anaesthesia.

Figure 2 shows the average deviations of threshold and response readings from the control with five of the phenothiazine derivatives under study.

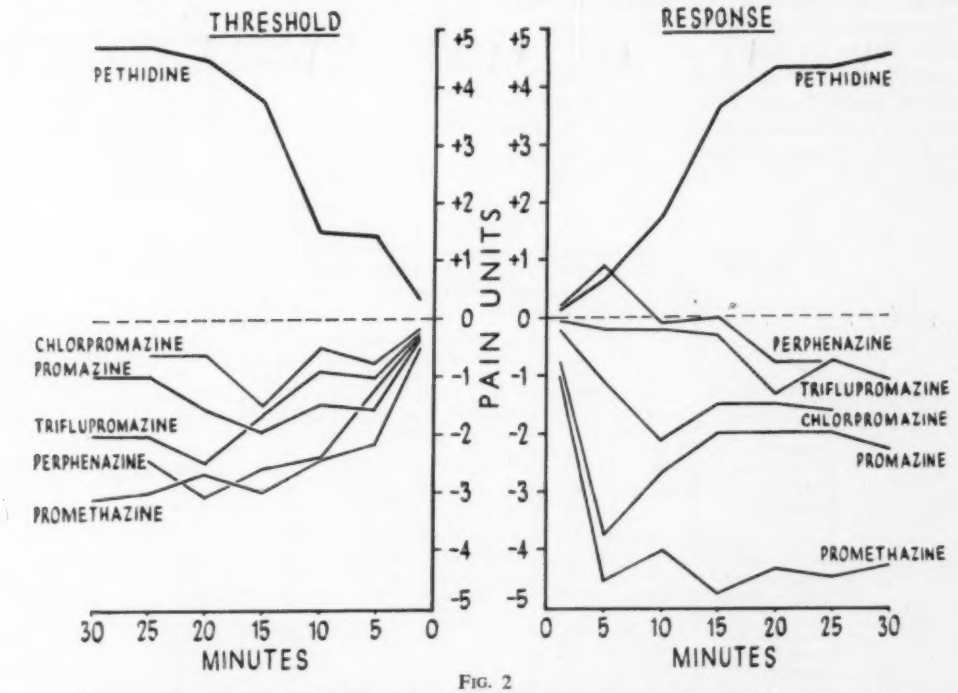


FIG. 2

Average alterations in pain threshold and response readings following the intravenous injection of several phenothiazines and comparison of these effects with that of pethidine 100 mg (For number of observations and dosage, see text.)

This represents the average of five observations with promethazine 50 mg and of two with each of the other drugs. The average of seven readings with pethidine 100 mg is included for comparison.

Bearing in mind the limitation of these findings it would appear that all the compounds studied increase sensitivity to pain and that this effect seems to be more marked with promethazine 50 mg than with the other drugs. The maximum "anti-analgesic" effect appeared about 20 minutes after intravenous injection but it was not possible to prolong the investigations and thus obtain an estimate of its duration of action. There was no correlation between the onset of restlessness and increased appreciation of pain, and in fact many patients had passed through the stage of extreme agitation and were calm and drowsy when the greatest decrease in pain readings was noted.

Intramuscular injection.

In these studies the phenothiazine derivatives were given in combination with atropine 0.6 mg, as pre-anaesthetic medication before the operation of uterine curettage. The patients were all of good physical status, conforming to the requirements of grades 1 and 2 risks of the American Society of Anesthesiologists' classification as described by Dripps, Eckenhoff and Vandam (1957).

Control readings in duplicate were made before injection of the drug and on two or more occasions before the induction of anaesthesia. It was observed that the peak effect of the phenothiazine derivatives occurs 75 to 90 minutes after intramuscular injection and it was necessary to make certain that readings were made at this time.

Since the actions of nine phenothiazine derivatives were studied and since two of these were studied at more than one dose level, it was not possible to present the findings in the same detail as for promethazine 50 mg in the earlier publication. We therefore calculated the percentage incidence of changes in both the threshold and response readings which we observed 75 to 90 minutes after administration of the phenothiazine derivatives. These are shown in table I, which also includes data for pethidine 100 mg to illustrate the different effects of the phenothiazine and analgesic drugs.

In order to arrive at a single figure for each drug, which would give some guide as to its analgesic or anti-analgesic action the "analgesia index" has been devised. This is calculated as follows:

$$\frac{\left(\begin{array}{c}\text{Incidence of increase}\\ \text{in readings}\end{array}\right)\text{minus}\left(\begin{array}{c}\text{Incidence of decrease}\\ \text{in readings}\end{array}\right)}{\text{Total number of observations.}}$$

TABLE I

Incidence of changes in pain threshold and response readings produced 75 to 90 minutes after injection of various phenothiazines and the "analgesia index" for these drugs. Data for 100 mg pethidine are included for comparison.

Drug	Dose (mg)	No. of patients	Percentage incidence of alteration in pain readings			Analgesia index
			Increase	No change	Decrease	
Chlorpromazine	50	11	22	70	8	+0.14
Trimeprazine	25	10	48	38	14	+0.34
Promazine	100	22	25	64	11	+0.14
Promazine	25	20	17	75	8	+0.09
Prochlorperazine	12.5	17	0	83	17	−0.17
Perphenazine	5	30	7	67	26	−0.19
Trifluperazine	1	9	0	67	33	−0.33
Triflupromazine	20	24	0	63	37	−0.37
Promethazine	50	56	2	30	68	−0.66
Promethazine	10	12	8	20	72	−0.64
Pecazine	50	11	0	27	73	−0.73
Pethidine	100	80	62	31	7	+0.55

It can be seen from table I, that none of the phenothiazine derivatives showed the same degree of analgesic action as pethidine. The findings in this table enable them to be classified into three groups as follows:

1. Those showing some analgesic activity, as judged by a positive analgesia index. (Chlorpromazine, trimeprazine, and promazine.)
2. Those with a mild anti-analgesic action, in which the majority of changes in readings fell within the accepted range of error of the method of analgesimetry but where analgesia index has a negative value. (Prochlorperazine, perphenazine, trifluperazine, triflupromazine.)
3. Markedly anti-analgesic drugs, with a preponderance of decrease in pain readings and a negative analgesic index. (Promethazine and pecazine.)

There was no significant difference in the distribution of the incidence of changes in readings between individual drugs in any of the above groups.

The average effect of each of the three classes of drugs is shown in table II, and it can be seen that each group is significantly different from the others. Lest it be thought that the title "some analgesic activity" ascribed to group 1 in this table suggests that it is composed of pethidine-like drugs, it is important to note that a highly significant difference in the incidence of alterations in pain readings exists between the effects of these phenothiazines and that of pethidine (table III). The number of observations with trimeprazine was too small to include in this analysis and the reasons for this paucity of cases have been explained (Dundee and Moore, 1961c).

TABLE II

Comparison of analgesic action of groups of phenothiazine derivatives, arranged according to scheme outlined in text.

Group	Class	Percentage incidence of alterations in pain readings			Analgesia index
		Increase	No change	Decrease	
1	Some analgesic activity	27	61	12	+0.15
2	Mildly anti-analgesic	3	69	28	−0.26
3	Markedly anti-analgesic	4	24	72	−0.68

Groups compared	Significance of difference between distribution of readings
1 and 2	$\chi^2 = 28.232$; df = 2; P<0.001
1 and 3	$\chi^2 = 93.006$; df = 2; P<0.001
2 and 3	$\chi^2 = 29.989$; df = 2; P<0.001

TABLE III

Comparison of the analgesic action of the group 1 phenothiazines with that of pethidine 100 mg.

Drug	Significance of difference of distribution of analgesic readings from those of pethidine 100 mg		
	χ^2	df	Probability
Chlorpromazine 50 mg	21.347	2	P<0.001
Promazine 100 mg	16.075	2	P<0.001
Promazine 25 mg*	8.952	1	P<0.01
All Group 1	35.962	2	P<0.001

* With promazine 25 mg it was necessary to pool two groups of effects (increase in readings and no change in readings).

The subdivision of phenothiazine drugs according to analgesic activity bears no relationship to the chemical subdivision in figure 1. A few comparisons of the effects of compounds differing only in one chemical group are shown in table IV. Although only the "analgesia index" is shown in this table, differences were calculated from the absolute figures which form the basis of table I.

It is unwise to draw too rigid conclusions as to the effect of chemical structure on clinical action from observations with a small number of drugs but we have definitely failed to substantiate the finding of Hougs and Skouby (1957) that chlorination increases the analgesic action of the phenothiazines. This is further shown by the presence of two chlorinated compounds (perphenazine and prochlorperazine) in group 2 as classified above, while the group of compounds showing most analgesic activity contained only one chlorinated phenothiazine. The action of fluorination in decreasing analgesic activity appears to be pronounced but observations with more compounds are needed before this can be stated with certainty.

The effect of replacing a dimethylaminopropyl side chain by a piperazine ring on the analgesic action of phenothiazines is not clarified by the data in table IV. It may be of some importance to note that all the piperazine-containing phenothiazines have been classed as having mild anti-analgesic activity in table I, whereas all the ones for which an analgesic action has been demonstrated have a dimethylaminopropyl side chain.

The present findings do not suggest any reason for the strong anti-analgesic action of promethazine, which is demonstrable even with a 10 mg dose. The consistency of this action is shown by the fact that the analgesic index is practically identical for 50 and 10 mg doses of promethazine and, as will be seen, this index was calculated from a fairly large series of observations with both doses. The writers are also unable to suggest any chemical relationship between promethazine and pecazine, which might be responsible for the similarity of their actions.

DISCUSSION

It is necessary to stress that the main findings in this paper apply to the effects of the phenothiazines as observed 60 to 90 minutes after intramuscular injection. They do not exclude the possibility of a biphasic reaction with an early increase in appreciation of pain followed by a later decrease. Clinical facilities did not permit the authors to carry out observations at longer time intervals. The findings are considered to be of importance to anaesthetists in that they reflect the changes in response to somatic pain which may be

TABLE IV

Comparison of effect of phenothiazines, which differ from each other in only one chemical group, on the patients' appreciation of pain.

Factors under study	Drugs compared	Analgesia index	Significance of difference
Dimethylaminopropyl	Trifluprornazine 20 mg	−0.33	
	Trifluperazine 1 mg	−0.37	$\chi^2 = 0.084$: df = 1*: $0.80 > P > 0.70$
v.			
Piperazine side chains	Chlorpromazine 50 mg	+0.14	$\chi^2 = 9.404$: df = 2: $P < 0.01$
	Prochlorperazine 12.5 mg	−0.17	
	Trifluprornazine + Chlorpromazine	−0.17	$\chi^2 = 3.709$: df = 1*: $0.10 > P > 0.05$
	Trifluperazine + Prochlorperazine	−0.23	
Chlorination	Promazine 100 mg	+0.14	
	Chlorpromazine 50 mg	+0.14	$\chi^2 = 0.250$: df = 2: $0.70 > P > 0.50$
Fluorination	Promazine 100 mg	+0.14	
	Trifluprornazine 20 mg	−0.33	$\chi^2 = 8.591$: df = 2: $P < 0.02$

* Paucity of numbers of cases showing a rise in readings necessitated pooling these with those in whom the drug had no appreciable effect on the pain readings. The significance levels were calculated from the incidence of readings which revealed an increase in sensitivity to pain as compared with the remaining observations.

anticipated with the drugs which are used for routine pre-anaesthetic medication.

These results show that minor alterations in the side chains attached to the phenothiazine nucleus can produce marked differences in their clinical actions. This is known to apply to the barbiturates, ethers, sulphonamides and many other widely used drugs. In the case of the barbiturates the effects of some of the side chains are fairly well understood but, apart from the decrease in analgesic activity produced by fluorination, this does not yet apply to the phenothiazine group. However, although this study is only concerned with one facet of their actions, it demonstrates that it is wrong to consider the phenothiazines as a group of compounds with qualitatively similar actions in which the more recently introduced compounds differ from chlorpromazine only in their potency and toxicity.

This study also prompts reconsideration of the action of the "lytic cocktail" consisting of pethidine, promethazine and chlorpromazine. Moore and Dundee (1961a) found that a mixture of pethidine 100 mg and promethazine 50 mg was almost devoid of analgesic activity and, from the present results it would not be expected that the addition of 50 mg chlorpromazine would enhance the analgesic action of this mixture to any significant degree. However, Smith and Fairer (1953) and Harrison (1955) reported that following the use of the lytic cocktail patients did not require any postoperative analgesic drugs for several hours. They stressed that the pain-free postoperative period was one of the advantages associated with its use. Vialard (1953) found that an infusion of pethidine and chlorpromazine eased pain in patients in whom the opiate alone was ineffective. In the light of the findings in this paper, these observations, together with the beneficial effects of the phenothiazines in obstetrics (including those classed in table I as being markedly anti-analgesic) suggest that the view that they produce a "pharmacological frontal lobotomy" as postulated by Terzain (1952). Detailed studies of the analgesic action of the pethidine, promethazine and chlorpromazine combination are in progress in order to clarify this point.

One of the most important clinical applications of the findings in this study is the effect of the pre-anaesthetic use of the phenothiazine compounds on the course of barbiturate anaesthesia. Dundee and Riding (1960) demonstrated that opiate premedication reduced the incidence of abnormal muscle movements associated with the use of thiopentone and Inactin. Subsequent investigations showed that anaesthesia with methohexitone (Brietal) was much more influenced by the type of premedication than were the two thiobarbiturates; compared with the use of atropine alone, pethidine very markedly lowers the frequency of muscle movements (Dundee and Moore, 1961a), whereas the anti-analgesic drugs promethazine (Moore and Dundee, 1961a), and hyoscine (Dundee and Moore, 1961b) increases both the incidence and intensity. In a study carried out concurrently with the present one, the authors found that the incidence of abnormal spontaneous muscle movements occurring following the injection of 1.6 mg /kg of methohexitone was directly related to the analgesic index of the phenothiazine derivatives used for pre-anaesthetic medication (Dundee and Moore, 1961c). The extent to which these findings apply to thiopentone has not yet been determined.

It is tempting to postulate some connection between the findings of these analgesic studies and the anti-adrenaline action of the phenothiazines. Gross et al. (1948) have demonstrated the analgesic effect of adrenaline in man, while Parson and Goetzl (1945) claimed that pain itself raises the pain threshold because of the release of adrenaline. Animal experiments by Goetzl, Burrill and Ivy (1944) showed that amphetamine intensifies morphine analgesia, while there are many convincing reports of the beneficial effects of combinations of amphetamine or dextroamphetamine with mild analgesics (Long, 1950; Coppersmith, 1951; Reed, 1956). An adrenolytic action has been claimed for most of the phenothiazine derivatives but comparative data concerning their potency in this respect is limited to the report of Eggers, Corssen and Allen (1959). Their finding that chlorpromazine has a more marked adrenolytic effect than promethazine, while the action of pecazine is intermediate between these two, cannot be correlated with the observations reported here on the anti-analgesic action of the drugs. It is not possible, however, to dismiss completely some, as yet unexplained, connection between these two facets of the action of the drugs.

SUMMARY AND CONCLUSIONS

Although there is some evidence in the literature to show that chlorpromazine potentiates the action of analgesic drugs, this has not been shown to apply to all the members of the phenothiazine group. This aspect of their actions has been studied by the authors, using a method of analgesimetry in which a measurable degree of pressure is applied to the anterior surface of the tibia until the patient experiences pain.

The findings suggest a division of the phenothiazines into three groups as follows:

1. Those having some analgesic activity: chlorpromazine, promazine, trimeprazine.
2. Those having slight anti-analgesic action: prochlorperazine, perphenazine, trifluperazine, triflupromazine.
3. Those having markedly anti-analgesic activity: promethazine and pecazine.

Several unsuccessful attempts were made to correlate the above grouping with the chemical structure of the drugs. Fluorination may decrease analgesic action to some extent.

The degree of analgesia produced by group 1 phenothiazines is not as marked as that produced by pethidine.

Some of the implications of these findings have been discussed.

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CORRESPONDENCE

MUSCLE PAINS AFTER SUXAMETHONIUM AND SUXETHONIUM

Sir,—The investigation reported by Burtles (*Brit. J. Anaesth.*, 1961, **33**, 147) showed no appreciable difference in the pain producing powers of these two drugs when used by a group of anaesthetists with differing techniques and anaesthetic drugs. In my investigation (*Brit. J. Anaesth*, 1959, **31**, 530) I tried at first to assess the results obtained by all our anaesthetists in a somewhat similar fashion, but found the results unreliable and certainly not comparable because of the wide variations in techniques, drugs, and of course in the skill of the anaesthetist. I therefore restricted my investigation to my own work entirely, in an attempt to obviate a large number of these variables.

Under these circumstances, therefore, it seems to me that the basis of my comparison made on patients I anaesthetized myself, when almost all the surgery was performed by one surgeon, and at times the two drugs compared on the same patient, is more reliable than that reported by Burtles.

I can state with confidence that the differences I observed have led me to use suxethonium in preference to suxamethonium whenever I require a short-acting relaxant.

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Brit. J. Anaesth. (1961), **33**, 432

THE CARDIO-OESOPHAGEAL JUNCTION

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ASPIRATION of gastric contents following regurgitation or vomiting is probably the most common serious accident to occur in connection with general anaesthesia. In a report of the Committee of the Association of Anaesthetists investigating deaths associated with anaesthesia (Edwards et al., 1956) it was established that aspiration of gastric contents was the most common single cause of death.

Fortunately not all instances of regurgitation or vomiting have a fatal outcome. Indeed, regurgitation may not be noticed. An investigation by Culver, Makel and Beecher (1951) showed that the actual incidence of regurgitation may be as high as 26 per cent. Similar results have been obtained by a number of recent investigators. A good representative survey is that of Berson and Adriani (1954) who report on 926 patients. They administered carmine red in gelatine-coated capsules with 15 ml of water half an hour before operation. The patients were routinely prepared and had been fasting for 8 hours. The pharynx of each patient was examined postoperatively and any dye present was aspirated. Ammonia was placed in the suction bottle and a colour change to purple indicated that dye and not blood was present. Berson and Adriani found an overall incidence of regurgitation of 14 per cent. In those intubated they found an incidence of 25 per cent. In those with a Ryle's tube they found an incidence of 23 per cent even though these latter patients were aspirated before induction and the tube was allowed to drain freely during the operation.

These figures alone lead to the inescapable conclusion that the cardio-oesophageal junction is of great concern to the anaesthetist.

MECHANISM OF THE CARDIO-OESOPHAGEAL JUNCTION

Many theories have been put forward to explain the normal one-way traffic at the cardio-oesophageal junction; some of these theories are patently untenable while none, the author feels, has been demonstrably conclusive.

Anatomical. Two and a half centuries ago Helvetius (quoted by Marchand, 1955) described an anatomical sphincter at this site but some modern anatomists doubt the existence of a sphincter as an entity. Lendrum (1937), who dissected 150 specimens, denied the existence of a sphincter, whereas Lerche (1950), who dissected 100 specimens, believed that a sphincter did exist. The large number of oesophagi which were dissected before a decision for or against the presence of a sphincter could be made would suggest that, even if present, the sphincter is not obvious and is unlikely to have the same sphincteric effect as the other clearly recognizable sphincters.

Crural compression. Chevalier Jackson (1922) claimed, and more recently others supported the view, that the diaphragmatic crura exert a pinch-cock effect. The compression of the lower oesophagus by the crural fibres has been claimed to account for the hold-up in a "barium swallow" during inspiration and the formation of what is radiologically termed the "phrenic ampulla". This might explain the efficiency of the junction during inspiration when the crura contract but not during expiration. Obviously when neuromuscular blocking agents are used during general anaesthesia the competence of the cardio-oesophageal junction cannot be dependent on extramural compression because the paralyzed crura can no longer actively contract.

Physiological sphincter. Payne and Poulton (1927) suggested that the lower end of the oesophagus possesses sphincteric action even though no anatomical sphincter could be displayed, and subsequently sphincter activity was demonstrated in parts of the gut remote from any anatomical sphincter. Radiographs taken to

demonstrate caustic injuries to the oesophagus lend some support to the sphincter theory. The stricture at the lower end of the oesophagus usually stops short of the gastro-oesophageal junction and a terminal segment is seen to be normally distensible. This is a constant finding which suggests that spasm of this segment occurs at the moment of injury and so itself escapes corrosion, though in so doing it causes severe injury to occur immediately above.

These three theories—anatomical, crural compression, and the theory of a physiological sphincter—have been advocated and refuted in the past. It is evident that no one of them alone can adequately explain the facts.

Modern view. In recent years a different approach has been made in an attempt to solve the problem. Before discussing the latest trends it is important to have clearly in mind the two facts which must be explained. Firstly, there is the question of the temporary delay at the cardio-oesophageal junction under normal conditions of swallowing. This has already been referred to as the "phrenic ampulla" seen radiologically during deep inspiration. Secondly, a convincing explanation must be found for the undoubted fact that under normal conditions food passes in one direction only from the oesophagus to stomach whether the subject be erect, horizontal or standing on his head.

Delay at cardio-oesophageal junction on swallowing.

During the screening of a "barium swallow" it may be observed that strong peristaltic waves passing down the oesophagus to within a few centimetres of the cardia fail to force the barium into the stomach during deep inspiration. The terminal oesophagus is caught between a distending force from above and a resisting force from below, hence the formation of the ampulla. These observations have been said to prove that the diaphragmatic crura compress the oesophagus and cause a hold-up of barium but Dornhorst, Harrison and Pierce (1954) have attributed this hold-up of barium to the pressure gradient between abdomen and thorax on inspiration.

The intrathoracic pressure is subatmospheric during quiet respiration varying from -10 cm H_2O during inspiration to -5 cm H_2O during expiration. The intraperitoneal pressure varies from $+5$ cm H_2O on inspiration to zero on expiration. These pressure changes are transferred respectively to the oesophagus and stomach and effect a pressure gradient of at least 15 cm H_2O across the gastro-oesophageal junction.

Marchand (1955) performed experiments to observe the effects of increased intraperitoneal pressure on the oesophagus filled with barium. He employed an inflatable rubber balloon held against the abdominal wall, inside an encircling bandage, in order to raise the intraperitoneal pressure. He was able to show by investigating patients with a therapeutic pneumoperitoneum that the balloon pressure had a direct linear relationship with the intraperitoneal pressure (fig. 1). His radiological observations were as follows:

(1) A phrenic ampulla was always formed when barium was swallowed with the balloon inflated to to a pressure of 60 to 80 cm H_2O.

(2) When the pressure in the balloon was increased to over 120 cm H_2O the passage of

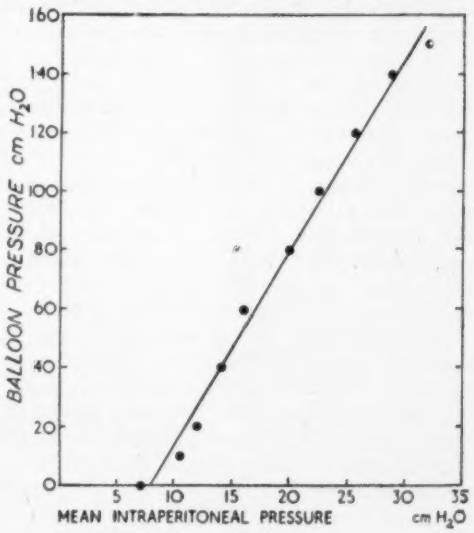

FIG. 1

Correlation of balloon pressures with mean intraperitoneal pressures. The peritoneal pressures were measured by inserting a needle into a pneumoperitoneal space and recordings were taken each time the balloon pressure was increased by 20 cm H_2O. (Reproduced from: Marchand, P. (1955), *Brit. J. Surg.*, **42**, 504.)

barium into the stomach was either prevented or else only achieved after vigorous peristaltic contractions had been evoked.

(3) When swallowing efforts were made against high intraperitoneal pressures, regurgitation from the stomach sometimes occurred and newly swallowed barium was forced back into the mouth.

Thus Marchand obtained visual evidence of delay in the oesophagus directly attributable to an increased pressure gradient.

Prevention of regurgitation.

It may be asked "Why does the pressure gradient, which is higher on the abdominal side and lower on the thoracic side effect delay to swallowing but not facilitate reflux or regurgitation from the stomach into the oesophagus?"

To help answer this, one may cite Barrett (1954), Dornhorst, Harrison and Pierce (1954) and Creamer (1955), who independently uphold the presence of a flap valve of mucous membrane which is situated at the exact point of junction of oesophagus and stomach. This valve is said to work by pouting the gastric mucous membrane at the lower end of the oesophagus. It depends for its efficiency on the normality of the underlying muscularis mucosa which moves the mucous membrane and causes it to pout into the orifice. Failure to identify the cardiac orifice when a thoracoscope was inserted into the stomach at laparotomy was said to lend support to the presence of this valve; and the absence of a dimple in the region of the oesophageal orifice when a patient with barium in the stomach was put in the head-down position was said to constitute additional supportive evidence.

More convincing evidence has been obtained to show that the angle at which the oesophagus enters the stomach is of considerable significance in preventing regurgitation. Allison (quoted by Barrett, 1954) showed in the following experiment that the angle of entry of oesophagus into the stomach was important in preventing regurgitation; he arranged on the necropsy table an oesophagus and stomach in normal relationship to each other and found that water pumped in at the pylorus was held up at the cardia. If the preparation was laid out as a bell with the oesophagus as handle then the cardia became incompetent.

Marchand (1955) performed an experiment on the stomachs of young male cadavers. He cannulated the pylorus and distended the stomach with water from a reservoir which was raised alongside a measured rule until the water was seen to escape from the oesophagus. He repeated the experiment for different positions of the stomach: (1) in the undisturbed position; (2) with the left dome of the diaphragm removed so that the fundus was increased and allowed to bulge up into the chest; (3) with the fundus excluded from the stomach by means of a clamp.

Table I shows the results of Marchand's experiments on the stomachs of cadavers. Interesting and illuminating as these figures undoubtedly are, from the anaesthetist's point of view they suffer from the disadvantage of being obtained from experiments on cadavers and not on anaesthetized subjects with an intact autonomic nervous system.

TABLE I

Intragastric pressure necessary to cause incompetence at cardio-oesophageal junction.

Position 1	Position 2	Position 3
28 cm H_2O	42 cm H_2O	9 cm H_2O

Position 1 is the undisturbed position of the stomach in a cadaver. In position 2 the left dome of the diaphragm is removed, allowing the fundus to bulge up into the chest. In position 3 the fundus is excluded from the remainder of the stomach by means of a clamp. From data in Marchand (1955) with the author's permission.

However, considering the radical character of this work it is understandable that it has not been applied to the living subject. It is not surprising therefore that the literature is devoid of quantitative information on the competence under anaesthesia of the cardio-oesophageal junction in relation to the oesophago-fundal angle. With this in mind it was decided to investigate the competence of the junction under anaesthesia and to observe what effect altering the oesophago-fundal angle would have on the competence of the junction.

COMPETENCE OF CARDIO-OESOPHAGEAL JUNCTION UNDER ANAESTHESIA

The work was carried out on fifteen patients on whom a laparotomy was performed under general anaesthesia. A Burge oesophageal tube, size 24 English catheter gauge, with a large inflatable cuff near the tip, was introduced through the

oesophagus into the stomach. When the presence of the tube in the stomach was identified by the surgeon the tube was withdrawn until it was felt to pass through the cardia. It was then further withdrawn until it came to rest 2 inches above the cardia. The cuff was next inflated with 50 ml of air and the open tube protruding from the mouth was connected to an underwater seal.

At this point a wide-bore needle or small cannula was inserted through the stomach wall so that its bevel lay within the cavity of the stomach: the other end of the cannula was connected by rubber tubing to a Y-shaped connection, one limb of which was connected to a mercury manometer and the other limb to an inflating rubber bulb (fig. 2).

By squeezing the bulb, a rise in intragastric pressure was effected. A clamp was placed across the pyloric region to prevent air passing into the small intestine. At a certain level of intragastric pressure the cardio-oesophageal "sphincter" became incompetent and air flowed from the stomach through the oesophageal tube and was seen to bubble under water. At the instant of "escape" the intragastric pressure was read from the mercury manometer. Three repeated "escape points" were determined and the three repeated observations were recorded.

The competence of the "sphincter" was investigated in three different positions of the stomach, A, B, and C (fig. 3), chosen to simulate as closely as possible the positions of the stomach in Marchand's investigations on cadavers. The positions were as follows:

(A) Normal position of the stomach allowing free expansion of the organ.

(B) Manual displacement of the stomach, upwards and to the left, by the surgeon so as to make

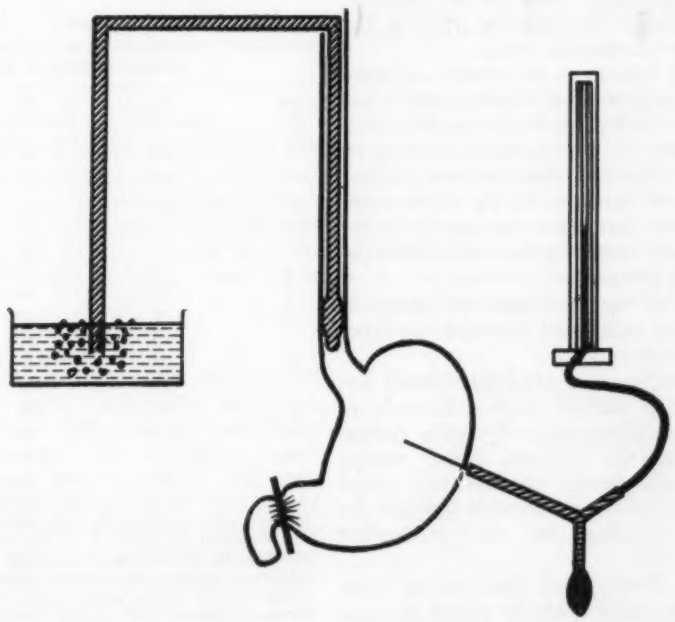

FIG. 2

The diagram illustrates the method used for investigating the competence of the cardio-oesophageal junction. An "escape point" is shown as air bubbling under water. Note the tip of the Burge tube situated 2 inches above the cardia and the clamp across the pylorus.

FIG. 3

A depicts the undisturbed stomach; B, the stomach displaced upward and to the left making the oesophago-fundal angle more acute; C, the stomach where the greater curvature is depressed making the oesophago-fundal angle less acute.

the oesophago-fundal angle more acute. This position resembled that obtained in Marchand's experiment when the left dome of the diaphragm was removed allowing the stomach to rise into the thorax.

(C) Downward traction on the greater curvature of the stomach so as to increase or make less acute the oesophago-fundal angle. This approximated to the position obtained by Marchand when he placed a clamp across the stomach from the left lip of the oesophago-gastric junction to the greater curvature, thereby excluding the fundus from the rest of the stomach.

The results of the experiment are shown in table II in which each figure represents the mean of three observations.

Every reading obtained when the stomach was pushed up and to the left (position B) was considerably higher than the corresponding reading for the undisturbed stomach. Every reading obtained when the greater curvature was pulled down (position C) was considerably less than the corresponding reading for the undisturbed stomach.

O'Mullane (1954) noted that manual compression of the stomach which resulted in a rise of intragastric pressure to 19 cm H_2O, failed to empty the gastric contents into the oesophagus. A study of the figures in table II shows that it is not so much the rise in intragastric pressure following compression of the stomach as the alteration in the oesophago-fundal angle, which determines the competence of the cardia.

TABLE II

Intragastric pressure necessary to cause incompetence at cardio-oesophageal junction.

Case No.	A (mm Hg)	B (mm Hg)	C (mm Hg)
1	38	49	13
2	14	25	4
3	12	14	5
4	12	21	1
5	24	27	4
6	12	22	10
7	13	33	3
8	18	47	4
9	42	52	5
10	28	38	11
11	43	82	2
12	29	87	11
13	29	38	10
14	29	39	19
15	57	87	11

Each reading in this table is the mean of three repeated observations. Position A is the normal undisturbed position of the stomach; position B is the stomach displaced upward and to the left making the oesophago-fundal angle more acute; position C is the stomach where the greater curvature is depressed making the oesophago-fundal angle less acute. In every instance the cardio-oesophageal junction was less competent when the greater curvature was depressed.

These figures were subjected to a statistical analysis and the result was as follows.

Mean differences between sites A, B and C respectively.

The variation between the three readings taken on individual patients at each of the three sites was not statistically significant; $P>0.05$ in the "t" test. Therefore the mean of the three was used for the purpose of calculating the group means of intragastric pressure at each of the three stated sites. The actual means and standard errors are as follows:

	Site		
	A	B	C
Means	26.7	44.1	7.5
S.E.	3.55	6.18	1.30

These means values were taken subjected to "t" tests of differences in the following terms:

A:B, A:C, B:C.

In each instance the difference was statistically significant; in the two latter items it was highly significant. The actual values are given below:

$A:B\ t = 2.44$
$P > 0.02$
$A:C\ t = 5.08$
$P < 0.001$
$B:C\ t = 5.80$
$P < 0.001$

It is apparent that the cardia is significantly less competent when the greater curvature is depressed making the oesophago-fundal angle more oblique (position C); on the other hand the competence of the cardia is significantly increased when the oesophago-fundal angle is made more acute (position B).

The anaesthetic technique.

The pre-operative medication consisted of promethazine 50 mg by intramuscular injection 1 hour before induction. (Promethazine was chosen because of its minimal vagolytic effect). Anaesthesia was induced with thiopentone and suxamethonium chloride and intubation was carried out using a cuffed endotracheal tube. Anaesthesia was maintained with a nitrous oxide and oxygen mixture and d-tubocurarine permitted controlled respiration using a non-rebreathing circuit. When the experiment was completed intravenous atropine was given and the pharynx was aspirated because of the excessive salivation which occurred when promethazine alone was used as premedication.

Cardio-oesophageal competence in hiatus hernia.

Two cases of sliding hiatus hernia were investigated to see if the competence of the cardia was similarly altered by change in position of the stomach. As in the experiments on normal subjects three repeated observations were taken and the mean intragastric pressure necessary to cause incompetence in each position of the stomach was recorded. The results are shown in table III.

TABLE III

Intragastric pressure necessary to cause incompetence at cardio-oesophageal junction.

Case No.	A (mm Hg)	B (mm Hg)	C (mm Hg)	Comments
1	12	8	3	Sliding hiatus hernia
2	17	11	2	Lax hiatus

Two cases of sliding hiatus hernia. A is the undisturbed position of the stomach; B, the stomach displaced upwards; C, the stomach where the greater curvature has been depressed. It is observed that when the stomach is displaced upwards in cases of hiatus hernia the cardio-oesophageal junction is less competent.

In both of these cases a lax hiatus was demonstrated at operation and, when the stomach was displaced upwards, part of the stomach was seen to slide into the hiatus and make the oesophago-fundal angle less acute (fig. 4). It was noted that the cardia was less competent when the stomach was displaced upwards instead of more competent as in the previous series. However, if in these cases of hiatus hernia the stomach position was

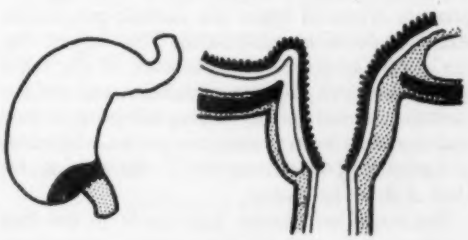

FIG. 4

The shaded area in the diagram on the right depicts that part of the stomach in a case of sliding hiatus hernia which occupies the oesophageal hiatus.

The diagram on the left shows part of the upward displaced stomach occupying a lax hiatus. It may be noticed that the oesophago-fundal angle has been obliterated.

translated into oesophago-fundal angle, it was observed once again that increasing the oesophago-fundal angle decreased the competence of the sphincter.

Dinnick (1961) observed a high incidence of regurgitation under anaesthesia in cases of hiatus hernia; the reduced competence of the oesophago-gastric junction noted above would help to explain this.

It can be objected that the readings were taken in anaesthetized and not conscious subjects. However, the author, being an anaesthetist, wished to obtain information on anaesthetized patients. A further objection is that as the subjects were anaesthetized there was no proof that the motor nerve supply to the stomach was functionally intact.

The integrity of this supply was presumed because promethazine alone was used in premedication and it was necessary subsequently to deal with the excessive salivation which resulted from the omission of a potent vagolytic drug.

Further in 8 cases due to have a vagotomy and pylorectomy the vagus nerve was stimulated immediately following the experiments. The oesophageal tube was passed into the stomach in order to record any rise in intragastric pressure and a circular electrode was clamped around the lower oesophagus. On stimulating the vagus well marked peristaltic waves passing over the stomach wall were observed, and a consistent rise in intragastric pressure of from 4 to 7 cm H_2O was recorded. When the vagus nerve was divided neither peristaltic waves nor a rise in intragastric pressure occurred when the central part of the sectioned nerve was stimulated. This showed that the results attributed to stimulation of the vagus were in fact due to nerve stimulation and not due to stimulation of the underlying oesophageal wall, and that the rise in intragastric pressure indicated a functioning motor supply to the part at the time of the experiments.

Reference has already been made to the high incidence of regurgitation under anaesthesia. Operations on the stomach itself and those in which the exploring hand of the surgeon palpates the viscus may well provide the alteration in oesophago-fundal angle necessary to effect regurgitation. For example, during a partial gastrectomy when the oesophagus and upper part of the stomach are drawn down prior to application of the clamp, the conditions are eminently favourable for regurgitation. It is suggested that in the case of abdominal surgery a cause of the high incidence of regurgitation has been demonstrated.

SUMMARY

The mechanism of the cardio-oesophageal "sphincter" is reviewed. Reference is made to Marchand's work on the stomach of cadavers. An experiment by which the author investigated the competence of the cardio-oesophageal junction in fifteen patients having a laparotomy under general anaesthesia is described. The motor nerve supply to the part was shown to be functionally intact during the experiment.

Increasing the oesophageal-fundal angle, by the palpating hand of the surgeon exploring the abdomen, was shown to decrease significantly the competence of the cardio-oesophageal junction.

Conversely, decreasing the oesophago-fundal angle significantly increased the competence of the cardio-oesophageal junction.

ACKNOWLEDGMENTS

Figure 1 appears by kind permission of the author and of the Editor of the *British Journal of Surgery*. I wish to thank Mr. Philip Lythgoe for his active help with this work; Dr. H. J. Brennan, Director of the Department of Anaesthesia, Manchester Royal Infirmary, for his encouragement with this research; Dr. R. Ollerenshaw of the Department of Medical Illustration; Miss Marion Russell of Christie Hospital for the statistical evaluation of the results; and finally Dr. A. R. Hunter for reading the manuscript.

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BERNARD JOHNSON MEMORIAL

On Wednesday June 28, 1961, in the presence of Mrs. Johnson, Sir Miles and Lady Clifford, representatives of the Middlesex Hospital and the Board of Faculty of Anaesthetists, Mr. J. B. Kinross formally unveiled the memorial plaque to the late Bernard Johnson in the main laboratory of the Research Department of Anaesthetics of the Royal College of Surgeons of England.

Dr. Geoffrey Organe, Dean of the Faculty, opened the ceremony with a reminder of the great services rendered to anaesthesia and to the Faculty by Mr. Bernard Johnson. He then called upon Mr. J. B. Kinross to unveil the commemorative plaque.

Mr. Kinross spoke as follows:

I feel greatly honoured to have been asked to unveil this Plaque to my friend, Bernard Johnson.

I only knew him for the last five years of his life, but, during those years, I came to know him intimately and it is due to him that I owe my interest in medical research.

This Department of Anaesthesia was his conception, and it is absolutely true to say that but for him there would be no such department in existence. Having persuaded his colleagues of the need, he proceeded to raise the necessary money—a self-imposed task which might well have been considered impossible. In just over two years of tremendous effort, he gathered together £120,000 and this research Department came into being.

But Bernard's work for Anaesthesia went far beyond this. He undertook lecture, demonstration and teaching tours throughout the Commonwealth and in Europe, and undoubtedly he did a great deal to raise the standards of Anaesthesia throughout much of the world. His conviction that British Anaesthesia was the best in the world was absolute; his determination that it should remain so and that it must be given every facility to grow became the task to which he devoted his energy.

He was also deeply interested in educational work and it is fitting that, apart from this Plaque, the funds of the Bernard Johnson Memorial Fund should be used to endow in perpetuity the Tutorship for Postgraduate Students.

There is no memorial, I think, which would have pleased him more than this Tutorship. For him, there was only one standard, and that was perfection. He felt that it was not enough for a student to know "How"—he must also know "Why". He was one of the most unselfish men I have ever known and he drove himself in the cause in which he believed so completely that in the end he gave his life for it when he was only fifty-four.

Most of us who are here knew Bernard and were his friends, and we rejoice to have this permanent Memorial with its fitting inscription, to a man who thought and planned for his profession on far-seeing and generous lines and who, by any standards, was a great man.

Of one thing I am certain: namely that Bernard would be both proud and happy to see this Department, as it is today, under the direction of his friend Ronnie Woolmer.

The plaque was then unveiled. It was made by Messrs. John Pinches, of carved oak, with lettering in gilt and with an inset portrait in bronze of Bernard Johnson. The lettering reads as follows:

BERNARD JOHNSON
1905–1959
F.R.C.S., F.F.A.R.C.S.
Hon. F.F.A.R.A.C.S.

Dean, Faculty of
Anaesthetists
1952–1955

A Devoted Servant
of Anaesthesia

Brit. J. Anaesth. (1961), 33, 440

THE PERFORMANCE OF A WALTON FIVE ANAESTHETIC MACHINE

BY

W. D. A. SMITH

Research Department of Anaesthetics, Royal College of Surgeons of England
London, W.C.2

THE Walton Five dental anaesthetic machine is designed to deliver known mixtures of oxygen and nitrous oxide. It has three controls: a mixture control, a pressure control, and an emergency oxygen control. The lever of the mixture control rotates around a scale calibrated in oxygen percentage. The markings are in 1 per cent divisions between 0 and 15 per cent, and at 20, 50 and 100 per cent. The pressure control is calibrated in mm Hg up to 20 mm. The pressure indicated at a given setting of the pressure control does not refer to the pressure at which the gas mixture is delivered. It refers to the pressure developed when the outlet of the machine is occluded. The emergency oxygen control is a sprung button.

Two safety devices are designed to prevent catastrophe in the event of failure of the oxygen supply. An automatic cut-off valve prevents the administration of nitrous oxide in the absence of an available oxygen supply; and an air inspiratory valve opens at a subatmospheric pressure, thus permitting the inspiration of air and preventing asphyxia in the absence of a gas supply. Failure of the nitrous oxide supply also results in the oxygen supply being cut off but under these circumstances oxygen may still be administered by depressing the emergency oxygen button.

One of these machines has been tested in the laboratory. The factors which were varied were the setting of the mixture control, the setting of the pressure control, the use of the emergency oxygen control, the "expiratory" resistance and the flow pattern. Both steady flows and simulated respiratory flow patterns were used. Measurements were made of the oxygen content of the gas mixture delivered and of pressures and flows.

METHODS

The measurement of oxygen concentration.

A Beckman D.2 paramagnetic oxygen analyzer was used for measuring the oxygen content of the gas mixtures. Its calibration was checked against Lloyd-Haldane and Schölander apparatuses, using various mixtures of oxygen and nitrogen. The gas mixtures delivered by the anaesthetic machine were sampled continuously by means of a small diaphragm pump, the analyzed sample being returned to the circuit under investigation. A given gas mixture was sampled for 2 minutes before a reading was taken. It was confirmed that any local pressure changes due to the sampling pump were not sufficient to affect the readings given by the oxygen analyzer.

The arrangement used for the measurement of the oxygen percentage in the delivered gas mixtures under steady flow conditions is shown in figure 1. Nitrous oxide and oxygen mixtures were delivered to a Heidbrink expiratory valve via corrugated tubing and they were sampled just proximal to the valve. The distal opening of the valve mount was occluded. Measurements of the oxygen content were made when the mixture control was set to 5, 10, 15, 20 and 50 per cent oxygen, while the pressure control was set to 5, 7.5, 10, 15 and 20 mm Hg, and while the expiratory valve was fully open and $\frac{1}{2}$ turn, 1 turn and $1\frac{1}{2}$ turns closed. The oxygen content of the delivered gas mixture was also determined while the emergency oxygen control was depressed, the mixture and the pressure controls being placed at different settings.

A versatile piston-type variable flow generator was used to represent a patient breathing into the system (Hill, Hook and Bell, 1961). The arrangement used for making measurements under simulated respiratory flow conditions is shown in figure 2. The generated flow waveform is indicated. The gas mixtures were delivered to a Heidbrink expiratory valve via a reservoir bag and corrugated rubber tubing. The expiratory valve was enclosed in order that the "expired" gas might be collected in a Douglas bag for sub-

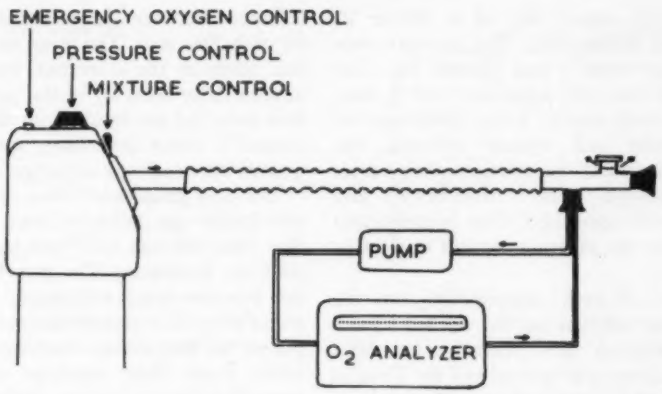

FIG. 1
The measurement of the oxygen concentration delivered under steady flow conditions.

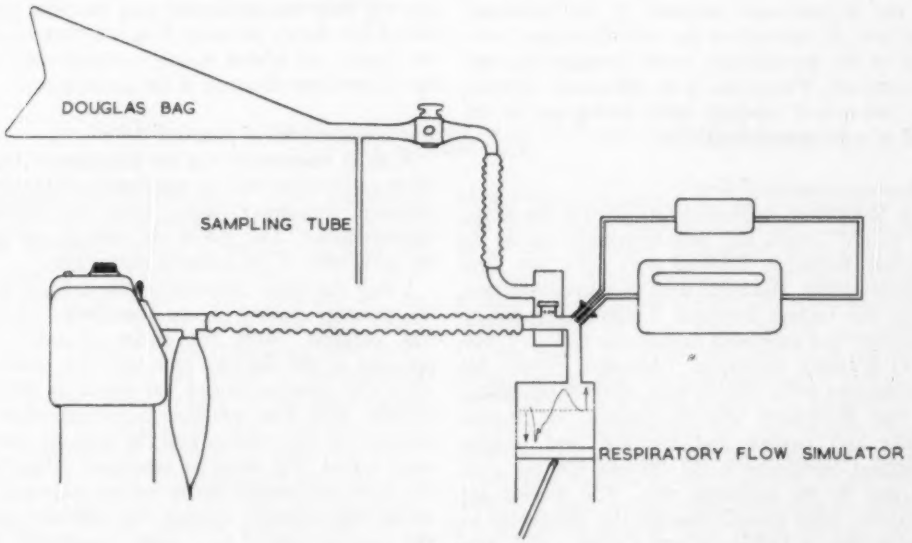

FIG. 2
The measurement of the oxygen concentration delivered under simulated respiratory flow conditions.

sequent analysis. A narrow-bore sampling tube was inserted between the tap and the Douglas bag. The distal end of the Heidbrink valve was connected to one limb of a wide-bore Y-piece. The other limb of the Y-piece was connected to the variable flow generator and the stem of the Y-piece was used for continuous sampling of "respired" gas mixtures.

Under simulated respiratory flow conditions measurements of oxygen percentage were made

when the mixture control was set to deliver 10 and 20 per cent oxygen only. The pressure control settings used were 5 and 10 mm Hg. The expiratory valve was used fully open and ½ turn, 1 turn and 1½ turns closed. Table I indicates the approximate tidal and minute volumes, the "respiratory" rates and the corresponding subsequently determined peak "inspiratory" and "expiratory" flow rates used. One measurement was made while the pressure control was set at 3 mm Hg.

At the start of each experimental run the Douglas bag was emptied and the tap was closed, so that the expiratory valve vented to air. After half a minute the tap was opened and the Douglas bag was filled with "expired" gas. The bag was again emptied and then finally filled with "expired" gas for subsequent analysis. Meanwhile the gas mixture was sampled continuously at the Y-piece and analyzed by the Beckman analyzer. At the end of the run the oxygen content of the gas mixture in the Douglas bag was determined. There was little difference between the two sets of readings taken during and at the end of each experimental run.

The measurement of flow.

A Rotameter, calibrated for air over the range 14 to 150 l./min, and flow transducers made by Vickers Research Limited were used for flow measurements. The latter were used in conjunction with the Vickers Research Limited Respiratory Analyzer and associated capacitance type ± 7 mm H_2O pressure transducer (Williams, 1960). An oscilloscope and a camera were used for recording.

The Rotameter was recalibrated for nitrous oxide and oxygen and nitrogen and oxygen mixtures containing 0, 20, 50 and 100 per cent oxygen in the following way. The known gas mixtures were passed through the Rotameter in series with a Parkinson and Cowan CD.1 gasmeter. For each gas mixture flows were adjusted to give Rotameter readings of 30, 50 and 100 l./min. Meanwhile, using a stopwatch, the time for a given volume of gas mixture to pass through the gasmeter was noted. The true flow rate was then calculated and the correction factor to be applied to the Rotameter reading for each of the gas mixtures at each of the flow rates used was determined. For a given mixture there was little difference between the correction factors derived for each flow rate. The mean of these was therefore taken as the correction factor for that gas mixture. The accuracy of the gasmeter at various flow rates had previously been checked at the Gas Council's meter laboratory, and it was subsequently adjusted and rechecked by the makers.

The flow transducers were then calibrated. Air and known gas mixtures were passed at steady flow rates through each flow transducer in series with the Rotameter. The true flow rates of each gas mixture were calculated, using the Rotameter correction factors derived above. The output of the Respiratory Analyzer was measured in volts. From these readings were derived the correction factors to be applied to the results obtained when using a flow transducer calibrated for air.

The experimentally determined correction factors for both the Rotameter and the flow transducers are shown in figure 3. It can be seen that the former are related mainly to the density and the latter to the viscosity of the gas mixtures.

The measurement of pressure.

A water manometer and the Respiratory Analyzer in conjunction with its associated ± 30 cm H_2O pressure transducer were used for pressure measurements. The water manometer was used for calibration of the pressure transducer.

Using the water manometer, the calibration of the pressure control of the anaesthetic machine was checked. With the outlet occluded, the pressure at the delivery tube was first measured while the pressure control was placed at different settings. Free flow was then permitted while the positions of the pressure and the mixture controls were varied. The pressure developed when these free flows were totally obstructed was measured. An initial high pressure reading was obtained before the pressure settled to a value comparable with that indicated by the pressure control setting. The contribution of the inertia of the water in the manometer to this initial reading was uncertain. Further measurements were therefore made, using the pressure transducer.

Neither continuous free flow nor complete obstruction is usual in normal use. The machine has to deliver gases against fluctuating flow resistances, the actual flow and pressure patterns being

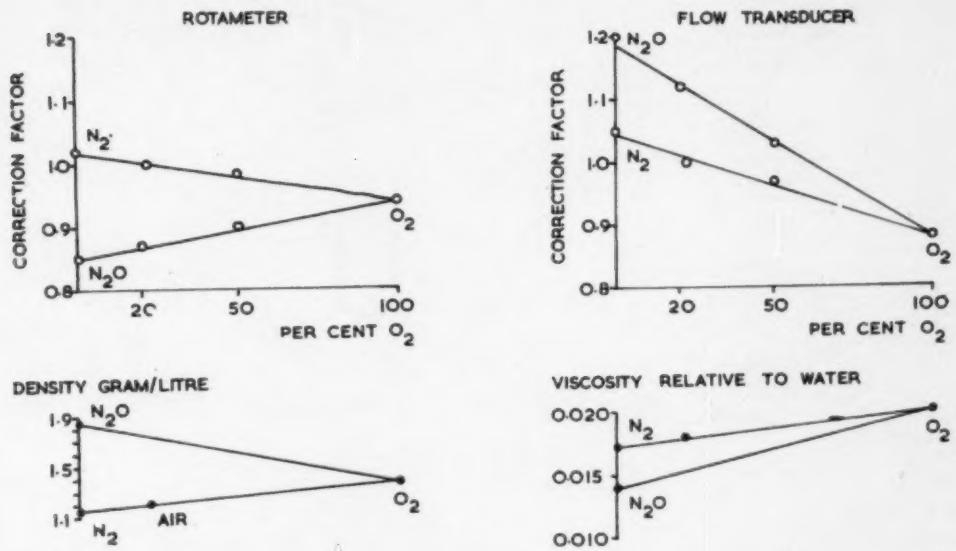

FIG. 3

The experimentally determined correction factors for the Rotameter and the flow transducer when calibrated for air.

governed by the characteristics of the anaesthetic machine, the characteristics of the expiratory valve at the particular setting at which it is used and the respiratory pattern of the patient. The pressures generated against the resistance of the expiratory valve under steady flow and under simulated respiratory flow conditions were therefore determined. For the former an arrangement similar to that shown in figure 1 was used, except that the water manometer was connected to a pressure tapping in place of the sampling tubes. Pressures were measured while the pressure control was set at 5, 10, 15 and 20 mm Hg, while the position of the mixture control was varied between the 0 and 100 per cent positions, and while the expiratory valve was open and $\frac{1}{2}$ turn, 1 turn and $1\frac{1}{2}$ turns closed. The method used for measuring the pressure swings occurring during simulated respiratory flow conditions is described below.

The measurement of pressure-flow characteristics.

The flow resistance characteristics of the particular Heidbrink valve used in this investigation were determined, both to air and to a mixture of 20 per cent oxygen with nitrous oxide. The Rotameter and the water manometer were used and the method was essentially that described by Mushin and Mapleson (1954). The flow resistance characteristics of the twin tubing supplying a nasal inhaler, and of the combination of the twin supply tubing and the expiratory valve incorporated with the nasal inhaler, were also measured.

For the determination of the pressure-flow characteristics of the anaesthetic machine under steady flow conditions, the 0 to 200 l./min flow transducer was used for flow measurement during free unobstructed flow. The Rotameter was used for measuring steady flows against resistance. The water manometer was used for pressure measurements. The experimental arrangement used is shown in figure 4. Throughout this experiment the mixture control was set to deliver 20 per cent oxygen with nitrous oxide. First, allowing free unobstructed flow, the flow rates were measured when the pressure control was set to 5, 10, 15 and 20 mm Hg. Then the occluded expiratory valve was connected to the outlet from the Rota-

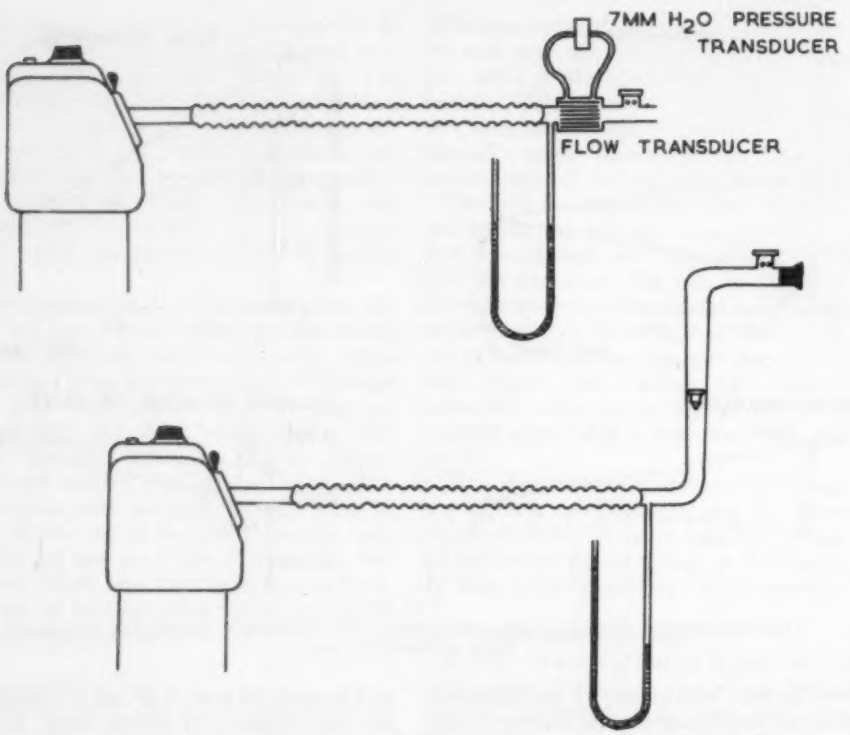

FIG. 4
The measurement of the pressure-flow relationships of the Walton Five under steady flow conditions. The flow transducer was used during free unobstructed flow.

meter. The flows achieved and the corresponding pressures generated were measured while the pressure control was again set to 5, 10, 15 and 20 mm Hg. The expiratory valve was used in the same open and partially closed positions as in the previous experiments. Finally, the pressures developed when the outlet was completely obstructed were confirmed for each setting of the pressure control.

Using the respiratory flow simulator the pressure-flow characteristics of the machine were then determined under tidal flow conditions. Transducers were used for both the pressure and the flow measurements. The experimental layout is indicated in figure 5. Measurements were made both with and without the reservoir bag in the circuit. The combinations of tidal volume and rate used were 500 ml at a rate of 13 per minute, 1,000 ml at a rate of 13 per minute, and 500 ml at a rate of 24 per minute.

The measurement of volume and "back-flow".

When measuring flow the output voltage from the Respiratory Analyzer is proportional to the flow passing through the flow transducer. The Respiratory Analyzer also has the electronic facility for integrating the "flow" voltages with respect to time, thereby offering a measurement of volume. This facility was used to determine the extent of the back-flow within the corrugated tubing during "expiration", thus giving an indication of the rebreathing to be expected. The flow transducer was inserted in the supply line as indicated in figure 6. The mixture control was set to deliver 20 per cent oxygen. The pressure control was set at 5 and 10 mm Hg only, since "rebreathing" was

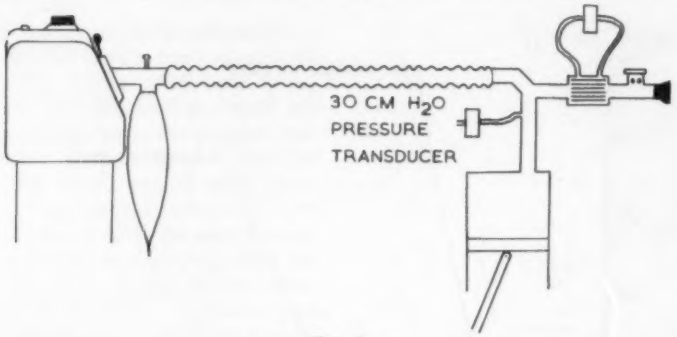

FIG. 5
The measurement of the pressure-flow relationships of the Walton Five under simulated respiratory flow conditions.

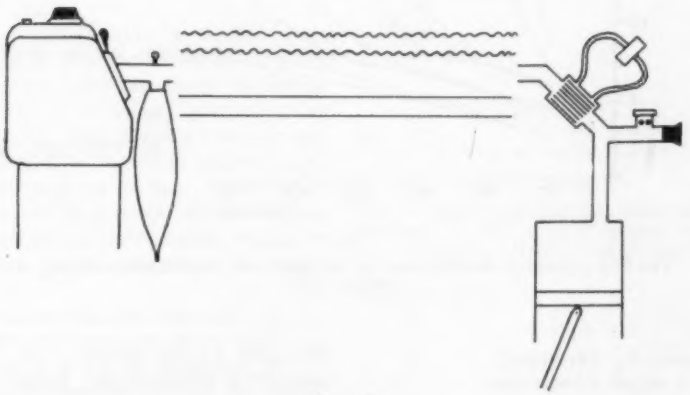

FIG. 6
The measurement of back-flow during simulated respiratory flow conditions, using corrugated and non-expansile tubing alternately, with and without the reservoir bag.

not observed when higher supply pressures were tried. The same expiratory valve settings and variations of tidal volume and of rate were used as in the previous experiment. An Ediswan pen recorder was used in place of the oscilloscope and the camera. Measurements were made both with and without the reservoir bag in the circuit. These were repeated after replacing the corrugated tubing by an equal length of non-expansile tubing.

RESULTS

The characteristics of the expiratory valve.

Since the characteristics of the particular expiratory valve used in this investigation are relevant to all the tests carried out, they are mentioned first. The pressure-flow curves obtained for this valve are shown in figure 7. The resistance of the valve in the open position is fairly representative for this type of valve. The resistance of the valve when partially closed, however, is high. The machine was therefore tested under correspondingly extreme conditions. The resistance of the valve to the nitrous oxide and oxygen mixture was greater than that to air, except at low flows.

The calibration of the mixture control.

The oxygen percentage delivered was always found to be the same for a given set of test con-

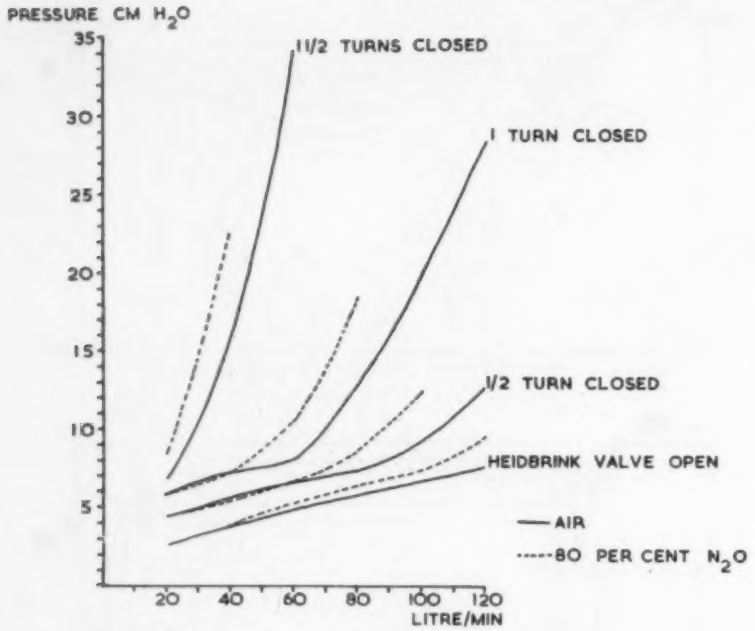

FIG. 7

The flow resistance characteristics of the Heidbrink valve used for testing the Walton Five.

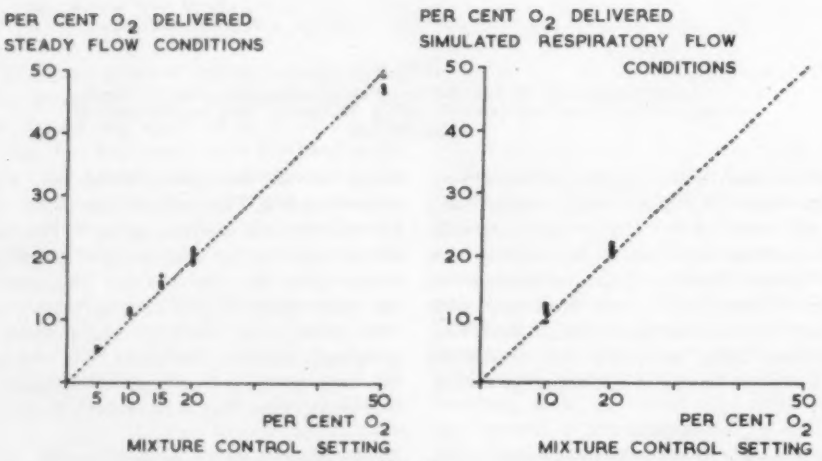

FIG. 8

The oxygen concentrations delivered, using different settings of the mixture control under all the conditions of testing.

ditions. The full spread of the measurements is shown in figure 8. The broken line indicates the ideal calibration. The readings of 19.5 and 19 per cent were obtained while the mixture control was at the 20 per cent setting, while the pressure control was set to 5 and 7.5 mm Hg, and while the Heidbrink valve was 1 turn and 1½ turns closed respectively. The solitary measurement of 9.5 per cent oxygen was obtained while the mixture control was placed at 10 per cent setting, while the pressure control was set at 3 mm Hg and while the respiratory flow simulator was adjusted to give a tidal volume of 300 ml at a rate of 18 per minute. All other oxygen percentage measurements within the range of normal use either coincided with or were slightly greater than the percentage indicated by the mixture control.

Whereas under steady flow conditions an increase in the resistance to flow, produced by screwing down the expiratory valve, was found to depress slightly the percentage of oxygen delivered, under simulated respiratory flow conditions an increase in the resistance to flow tended to cause a slight rise in the percentage of oxygen. Under both steady flow and tidal flow conditions an increase in the setting of the pressure control tended to cause an increase in the percentage of oxygen delivered.

The effect of depressing the emergency oxygen control upon the percentage of oxygen delivered is shown in figure 9. It can be seen that, subject to the setting of the mixture control, the higher the setting of the pressure control the less the effectiveness of the emergency oxygen control. With the pressure control set at 5 mm Hg, the percentage of oxygen delivered while the oxygen button was depressed was always greater than 75 per cent, regardless of the position of the mixture control. The Heidbrink valve was in the open position throughout this experiment.

The calibration of the pressure control.

With the mixture control set at 20 per cent oxygen, the pressures developed at different settings of the pressure control under the test conditions already described are shown in figure 10. When the outlet was kept occluded no pressure was measurable until the control was advanced up to nearly 2 mm Hg. The pressure fluctuated 1 cm H_2O above and below the mean value at a rate

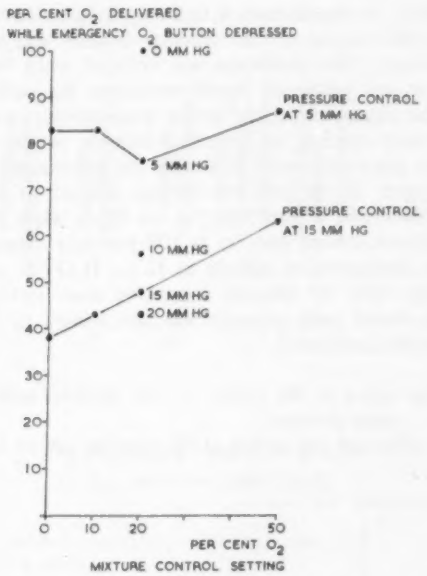

FIG. 9

The oxygen concentration delivered against the resistance of the open Heidbrink valve while the emergency oxygen control was depressed.

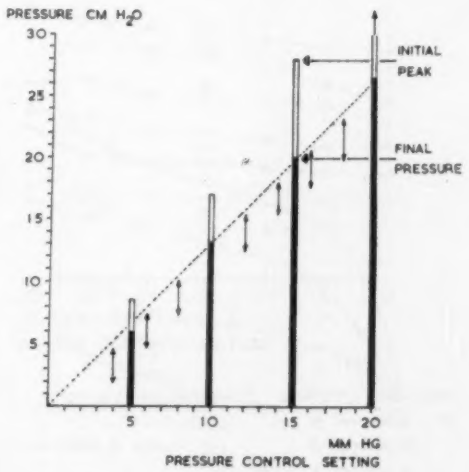

FIG. 10

The calibration of the pressure control. Vertical arrowed lines indicate pressure swings during maintained occlusion of the outlet. A pressure transducer was used for measuring the initial peaks.

which increased from 4 to 24 cycles per minute as the setting of the pressure control was increased. This oscillation was reduced when free flow was permitted before occluding the outlet. The magnitude of the initial steep pressure rise, already referred to, increased with the setting of the pressure control and with the percentage of oxygen. If the pressure control was set to any mark above 5 mm Hg (6.8 cm H_2O) while the mixture control was set at 100 per cent oxygen, the pressure rose initially to 41 cm H_2O (30 mm Hg); with the mixture control at other settings the initial peak pressure was also related to the speed of occlusion.

The effect of the setting of the mixture control upon pressure.

Although the setting of the mixture control had negligible effect upon the pressures developed during no-flow conditions, this was not found to be the case during steady flow conditions. Figure 11 reveals that for a given flow resistance and a given setting of the pressure control, the pressure within the anaesthetic circuit was increased as the percentage of oxygen was increased.

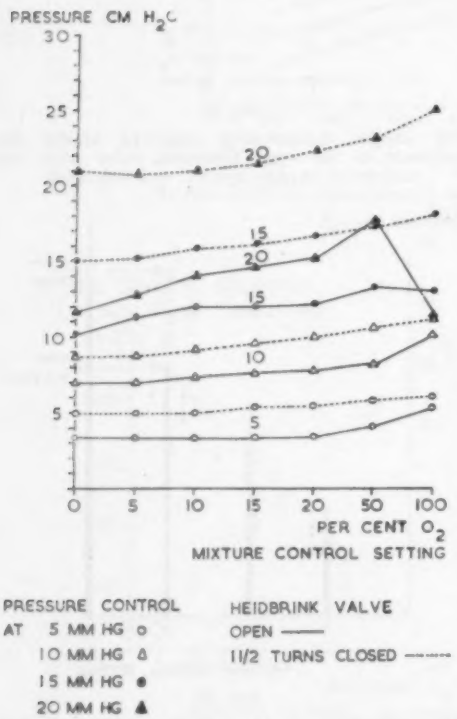

FIG. 11

The effect of the setting of the mixture control upon pressure (steady flow conditions).

Depression of the oxygen button during steady conditions.

When the emergency oxygen control was depressed while the outlet was occluded, the pressure settled between 40 and 41 cm H_2O (30 mm Hg), regardless of the setting of the mixture control. Trying different settings of the mixture control during steady flow conditions, however, a variable pressure increase was found when the oxygen button was depressed. This is shown in figure 14, and it is also referred to below under the heading of "pressure-supply-flowrate characteristics".

The pressures occurring during tidal flow.

Figure 12 shows the pressure swings that were observed during simulated respiratory flow, while the pressure control was set at 5 mm Hg and at 15 mm Hg, while the Heidbrink valve was open, and while the tidal volume, the "respiratory" rate and the mixture control setting were varied. The probable explanation of the discrepancies between figures 11 and 12 is that the valve settings were not identical, the two experiments having been performed on different occasions. There was a tendency for the pressure to rise as the oxygen percentage was increased, except that there was sometimes a fall of pressure upon reaching the 100 per cent oxygen position of the mixture control. In all cases there was an increase of pressure, of up to 2 cm H_2O, upon depressing the emergency oxygen button. As might be expected, both the mean pressures and the pressure swings varied with the tidal volumes and with rate.

Figure 13 shows the effect of closing the expiratory valve and of increasing the setting of the pressure control while other factors are kept constant (mixture control at 20 per cent oxygen; tidal volume of 750 ml; rate of 13 per minute). An increase of either causes an increase both in the mean pressure and in the pressure swing.

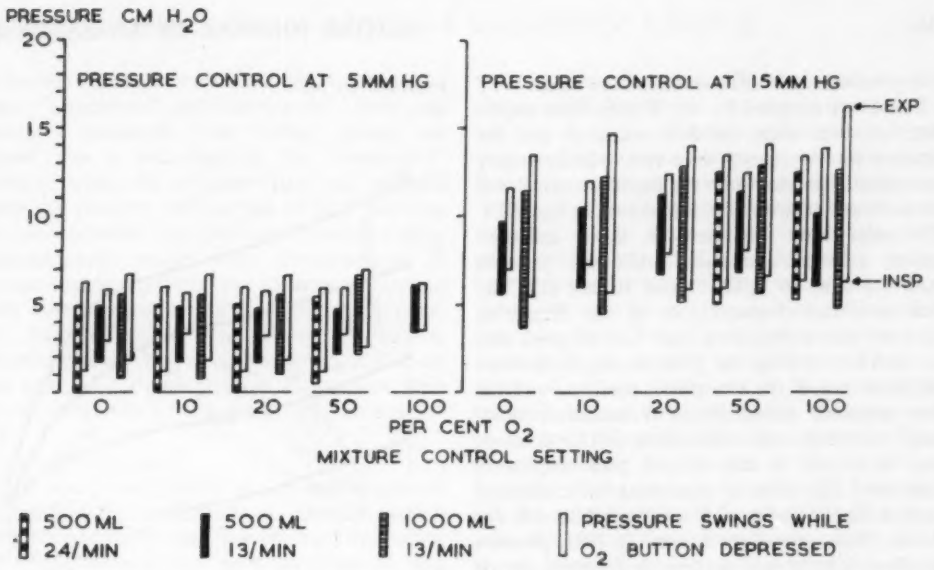

FIG. 12

The pressure swings occurring during various simulated respiratory flow conditions, the Heidbrink valve being open.

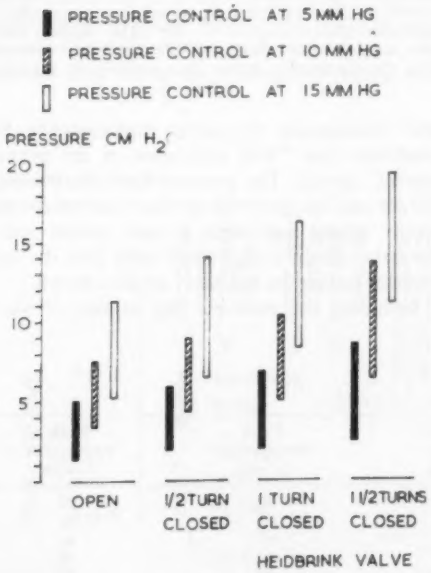

FIG. 13

The effect of varying the resistance of the expiratory valve, and of the setting of the pressure control, during set simulated respiratory flow conditions.

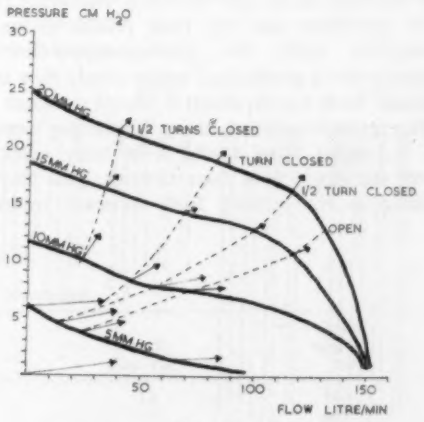

FIG. 14

The pressure-supply-flowrate characteristics of the Walton Five (solid lines) related to the flow resistance characteristics of the Heidbrink valve (broken lines) under steady flow conditions. The arrow points indicate the pressure-supply-flowrate characteristics while the oxygen button is depressed.

The pressure-supply-flowrate characteristics.

The flows supplied by the Walton Five anaesthetic machine when the flow resistance and the pressure control setting were varied under steady flow conditions, and while the mixture control was set to 20 per cent oxygen, are shown in figure 14. The solid lines indicate the flows delivered against different resistances while the pressure control was set to 5, 10, 15 and 20 mm Hg. The flow resistance characteristics of the Heidbrink valve are shown in broken lines. This diagram may be used for relating the pressure-supply-flowrate characteristics of the anaesthetic machine with the flow resistance characteristics of associated equipment, and both, with reservations indicated below, may be related to any defined peak respiratory flow rates. The effect of depressing the emergency oxygen control under each set of conditions is also shown. This caused an increase in both pressure and flow. The oxygen percentage delivered during depression of the emergency oxygen control was measured in order that the appropriate corrections might be made to the Rotameter readings.

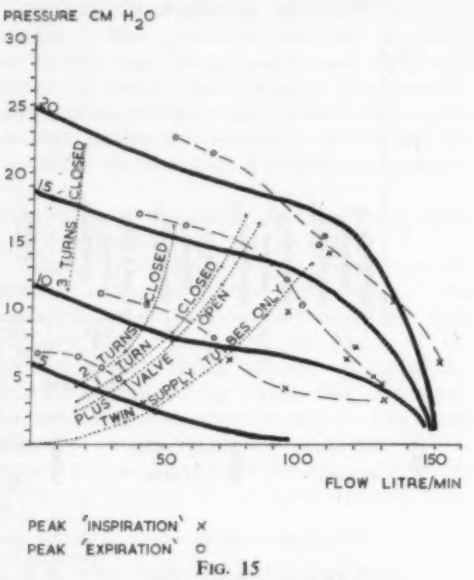

FIG. 15

The pressure-supply-flowrate characteristics under steady flow conditions (solid lines) and under tidal flow conditions (broken lines). In dotted lines are shown the resistance characteristics of the twin supply tubing for a nasal inhaler when used alone and in conjunction with the expiratory valve incorporated in the nosepiece.

The pressure-flow characteristics during tidal flow.

By allowing for the peak "inspiratory" and "expiratory" flows produced by the respiratory flow simulator (see table I), the flows delivered by the machine during the simulated respiratory peak flow conditions and the peak pressures can be compared with the pressure-supply-flowrate characteristics determined under steady flow conditions. Such a comparison is shown in figure 15. The pressures recorded during "expiration" tended to be higher than would have been expected from the steady flow characteristics. This may be related to the initially high pressures recorded upon obstructing the outlet under steady flow conditions (see "The calibration of the pressure control" above). The pressure-flow characteristics (20 per cent oxygen with nitrous oxide) of the twin supply tubing used with a nasal inhaler and of the nasal inhaler's expiratory valve (not the valve used for testing the machine) are also shown.

Including the reservoir bag in the circuit, or

TABLE I

Simulated respiratory variables.

Tidal volume ml	Rate per min.	Minute volume l./min	Peak "inspiration" l./min	Peak "expiration" l./min
500	13	6.5	33	20
750	13	9.8	48	32
1000	13	13	65	41
750	16	12	62.5	38
300	18	5.4	32	20
500	18	9	49	32
500	24	12	62.5	38
300	24	7.2	not measured	not measured

excluding it, made very little difference to the peak "inspiratory" and "expiratory" flows and pressures measured. The greatest change observed was a reduction in the "inspiratory" pressure when the reservoir bag was excluded while the pressure control was set to 5 mm Hg. On one occasion the pressure became slightly subatmospheric under these circumstances. At greater supply pressures the differences between peak values recorded with and without the reservoir bag in circuit were barely measurable. Examination of the records, however, did reveal that nearly all minor pressure fluctuations were smoothed out when the reservoir bag was used.

Back-flow.

The unexpected results of this experiment are displayed in figure 16. With the pressure control set at 10 mm Hg, reverse flow occurred only when the expiratory valve was very nearly closed, and then it was negligible. Only the results obtained while the pressure control was set to 5 mm Hg have therefore been given. There was not a great deal of difference between the reverse flows recorded under the four sets of conditions—corrugated tubing with and without the reservoir bag, and non-expansile tubing with and without the reservoir bag. Using the corrugated tubing, the reverse flow was only slightly greater when the reservoir bag was in the circuit than when it was not. A larger difference was expected. It was suggested that much of the reverse flow might have been taken up in expanding the corrugated tubing. Using non-expansile tubing, however, the reverse flow was often greater than when corrugated tubing was used, and sometimes it was greater when the reservoir bag was excluded from the circuit than when it was included. This effect has not been fully investigated, but careful scrutiny of the records revealed that when the reverse flow was greatest in the presence of the reservoir bag, it occurred during the early part of "expiration" only. This was expected. When the reverse flow was greatest in the absence of the reservoir, however, it was prolonged throughout the greater part of "expiration". This suggests that the reverse flow occurs as the result of an intermittent leak within the anaesthetic machine.

Other observations.

No deliberate tests were carried out to determine the precise performance of the safety devices, but at one time or another they were brought into action during this investigation and found to be working satisfactorily.

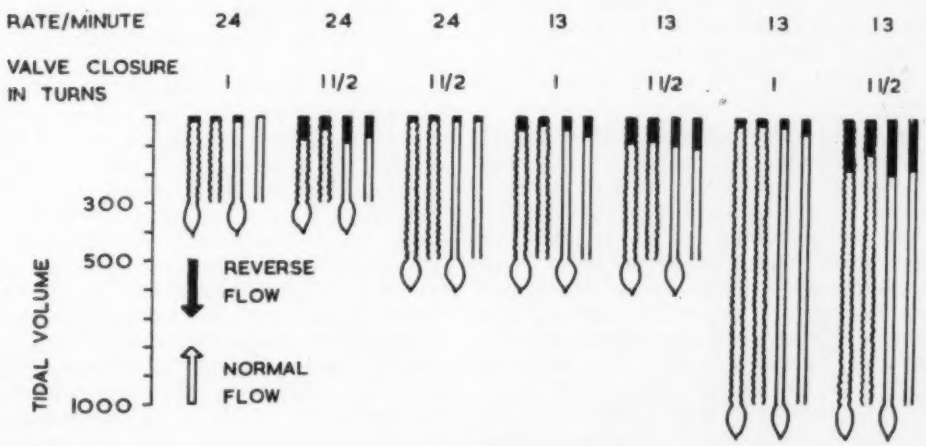

FIG. 16

The back-flow occurring during simulated respiratory flow conditions, using corrugated and non-expansile tubing alternately, with and without the reservoir bag. The pressure control was set to 5 mm Hg.

It was observed that when the pressure control was in the off position a very slight flow of oxygen still occurred. This was revealed by a small but measurable increase in pressure which eventually built up when the outlet was left occluded while the pressure control was in the off position. When the outlet was not occluded there was an increase in the oxygen concentration of the gas in the corrugated tube, to well above 20 per cent, when the pressure control was left in the off position.

DISCUSSION

The purpose of this investigation was to determine the performance of a particular Walton Five dental anaesthetic machine as a preliminary to using it for a specific experimental project. The steady flow tests were carried out because they were relatively simple. The simulated respiratory flow pattern tests were carried out because the assessment of any machine should include tests carried out under controlled circumstances comparable with those under which it would be used—unless it can be shown that simpler tests are adequate. In the absence of data on the respiratory patterns which actually occur during dental anaesthesia, the choice of the "respiratory" variables was arbitrary. Although the original intention was not to cast judgment upon the machine, a few comments will be offered.

The performance of this machine does live up to the claims published in the manufacturer's leaflet.

The usual, and probably the most serious, criticism of dental anaesthetic machines concerns the inaccuracy of the calibration of their mixture controls. There is no doubt about the calibration of the mixture control of this machine, even under extreme testing conditions, being a very considerable improvement over the calibration of many machines in current use, such as those tested by Goldman (1958), by Hunter and Fraser (1959) and by Bourne (1960). The calibration may give all the accuracy that clinical circumstances require but to acknowledge this would imply that the required accuracy has been defined. Pask (1960) has drawn attention to the precipitous arterial oxygen deprivation that may be expected when the inspired oxygen concentration falls to about 7 per cent. A case might therefore be made for a very high order of accuracy of the calibration of the mixture control in the 5 to 10 per cent oxygen region.

The effects and the possible dangers of raised airway pressures during dental anaesthesia in sitting patients do not appear to have received much consideration. Since they may be of some importance, attention has been paid to the pressures which may be generated by the Walton Five anaesthetic machine. The findings are reported but opinion as to their significance is reserved.

From the observations made upon the extent and circumstances of back-flow during "expiration", it is evident that any opinions expressed with regard to the effects of using, or of not using, a reservoir bag in conjunction with a dental anaesthetic machine should be viewed with caution.

The economics of using the Walton Five should also be considered. It can be seen from figures 14 and 15 that high flows, with correspondingly high gas consumption, are easily obtainable. Flows used in practice depend upon the patient's respiratory pattern, upon the apparatus used in conjunction with the anaesthetic machine, and upon the anaesthetist. If narrow-bore twin supply tubing is used to connect the anaesthetic machine to the nasal inhaler, then, if inspiration against resistance is to be avoided, the supply flow rate should be sufficient to meet the peak inspiratory demand of the patient. If wide-bore tubing of negligible resistance is used without a reservoir bag, then the supply flow rate should still be sufficient to meet the peak inspiratory demand. In the first case, however, the pressure control will have to be turned up higher than in the second. If the wide-bore tubing is used with the reservoir bag in circuit, and if unobstructed nasal breathing is fully established, then the supply flow rate need not be appreciably greater than the patient's minute volume. In practice, however, fine control of flow rate by manipulation of the pressure control at the lower end of the scale is not easy. (The calibration of the mixture control at such low flows was not checked.) If there is an air leak between the mouth and the pharynx during nasal breathing, then the pressure control should be turned up sufficiently to overcome the resistance of the nose and nasopharynx at the peak inspiratory flow rate. It will be appreciated that the more the pressure

control is turned up the greater will be the gas wastage and the airway pressure during expiration. It is suggested that the use of wide-bore tubing is indicated and that easy control of low flow rates, without sacrifice of the accuracy of the mixture control calibration, would be advantageous.

SUMMARY

The operational controls and the safety devices incorporated in a Walton Five anaesthetic machine are outlined. Some methods are described for testing the performance of such a machine in the laboratory. The results obtained upon applying these tests are reported. Attention has been given to the percentage of oxygen delivered, to the pressure-flow relationships of the machine when subjected to various external resistances under varied steady flow and simulated respiratory flow conditions, and to "rebreathing". The performance of this machine was found to be consistent with the claims of the manufacturer. The accuracy of the mixture control calibration which manufacturers should be asked to provide, and the significance of airway pressures, are questioned. The pressures and gas flows required in practice are considered.

ACKNOWLEDGMENTS

I wish to thank Professor R. F. Woolmer for providing every encouragement and facility. I am also indebted to Miss D. C. Casselle for carrying out the Lloyd-Haldane and the Schölander gas analyses. Mr. C. P. Henshilwood and Mr. Sharman of the Meter Laboratory, Watson House, very kindly checked the calibration of the gasmeter. The British Oxygen Company has given every co-operation and I am particularly grateful for the loan of the Walton Five dental anaesthetic machine. The work was carried out while holding a Wellcome Research Fellowship at the Research Department of Anaesthetics of the Royal College of Surgeons. The Wellcome Trust also purchased the Respiratory Analyzer.

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PROLONGED APNOEA DUE TO SUXAMETHONIUM

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IN many cases of "suxamethonium apnoea" described in the literature, it is probable that other factors were more directly concerned in the production of the apnoea than simply a prolonged action of suxamethonium (Wolfers, 1952; Grant, 1952).

The causes of prolonged apnoea have been well reviewed recently by Churchill-Davidson (1959) who advocated a rational approach to the diagnosis and treatment.

In order to implicate a muscle relaxant as the causative factor in a case of prolonged apnoea, it is necessary to demonstrate that a neuromuscular block actually exists. The technique for this has been described by Churchill-Davidson and Wise (1960), and involves faradic stimulation of motor nerves and observation of the responses of the muscles concerned.

In contradistinction to the non-depolarizing group of muscle relaxants, a reliable antidote is not available for reversing the effects of the depolarizing group and is usually not required as the normal duration of action of suxamethonium is so brief. Nevertheless there are rare and usually unexpected occasions when the action of suxamethonium is extended beyond that which might reasonably be expected. These prolonged effects may arise in three ways:

(*a*) Following repeated doses of suxamethonium, when the total amount administered is of the order of 1 to 1.5 g the dual block effect may develop.

(*b*) Following a single dose of suxamethonium, the duration of action may be extended from the normal 3 to 4 minutes to 10 to 20 minutes. This may be termed an extended response.

(*c*) Following a single dose of suxamethonium, the duration of the apnoea may be prolonged up to 1 to 3 hours. This may be termed a prolonged response.

Many workers have reported that a dual block effect may be produced by repeated doses of suxamethonium (Brennan, 1956; Hodges and Foldes, 1956) and these changes have now been demonstrated electromyographically (Churchill-Davidson and Christie, 1959). The various mechanisms that may account for this will be discussed later.

When the response to a single dose of suxamethonium is extended to 10 to 20 minutes, it was shown by Evans and his colleagues (1952) that the duration of the neuromuscular block could be correlated closely with the pseudocholinesterase level. In two cases described by them the pseudocholinesterase levels were normal and the possible explanation for this will be discussed later. It was shown that if the level was artificially raised by an infusion of concentrated pseudocholinesterase, the duration of the apnoea produced by a single dose of suxamethonium could be reduced (Evans et al., 1953). There have since been many reports in which an extended response to a single injection could be related to a reduction in the serum pseudocholinesterase. Apart from liver disease, malnutrition, and insecticide poisoning, a low pseudocholinesterase level may be found in healthy persons as part of a familial disposition (Kaufmann, Lehmann and Silk, 1960). Whilst it is reasonable to suppose that an extended response may be caused by a reduction in the speed of breakdown of suxamethonium, providing there is some esterase activity, it is difficult to understand how the action can be prolonged for hours, rather than minutes (Paton, 1958).

However, it is conceivable that where there is an electrolyte imbalance some change may take place at the neuromuscular junction, which leads to a reduction in sensitivity to depolarizing drugs. This mechanism might explain the case described by Hodges (1955), in which the pseudocholinesterase level was extremely low and follow-

ing a dose of 100 mg a prolonged apnoea resulted. Yet subsequently this patient was given a suxamethonium drip without untoward effect when the pseudocholinesterase level was normal. It is difficult to exclude other factors, however, that may have contributed to the prolonged apnoea.

A reason for believing that a low pseudocholinesterase level per se is not the cause of a prolonged response is that cases have occurred in which the pseudocholinesterase levels were normal (Argent, Dinnick and Hobbiger, 1955); also, many cases showing such a response have a higher pseudocholinesterase level than those cases that have shown only an extended response. Thus some other mechanism must be postulated to explain the prolonged action following a single dose of suxamethonium.

It has been shown that there are two types of pseudocholinesterase, typical and atypical (Kalow and Genest, 1957). These behave differently towards suxamethonium, in that in the concentration present in the plasma after a single injection, the atypical form of pseudocholinesterase has no action on suxamethonium (see fig. 1).

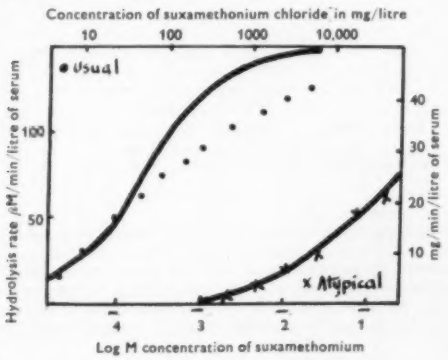


FIG. 1

Hydrolysis rate of suxamethonium by typical and atypical pseudocholinesterase at pH 7.0 and 30°C, after Kalow (1959).

If a dose of 100 mg is injected intravenously into an adult who has a plasma volume of 3.5 l., and the drug is evenly distributed in the plasma, the drug concentration would be less than 30 mg/l. As seen from figure 1, at this concentration atypical pseudocholinesterase has no action, whereas normal pseudocholinesterase would hydrolyze approximately 15 mg of the drug per minute per litre serum (i.e. approx. 50 mg/min in a normal adult).

In order to differentiate between these two forms of pseudocholinesterase, Kalow and Genest (1957) have devised a method which is based on the use of a pseudocholinesterase inhibitor. Various inhibitors are known, such as neostigmine, suxamethonium itself and local anaesthetic drugs. In this test dibucaine (Nupercaine) is used because it has an immediate inhibitory effect. The difference in the esterase activity after inhibition by dibucaine can be seen in figure 2.

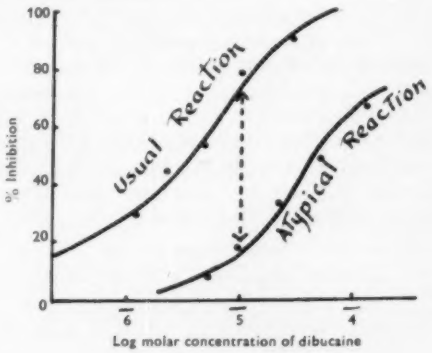


FIG. 2

Inhibition of typical and atypical pseudocholinesterase by varying concentrations of dibucaine, after Kalow and Genest (1957).

Figure 2 shows that at a -5 log molar concentration of dibucaine, there is a marked difference between the behaviour of typical and atypical pseudocholinesterase. Using this test, every person can therefore be given a dibucaine number, which is defined as the percentage reduction in esterase activity in the presence of a -5 log molar concentration of dibucaine under standard conditions. Persons with typical pseudocholinesterase have a high dibucaine number, usually around 74, whilst those with only atypical pseudocholinesterase have a low dibucaine number, under 20. It is possible to recognize a third group of people who have both typical and atypical pseudocholinesterase and in these the dibucaine number lies between 40 and 70. It is possible that in the presence of a relative overdose these are the patients who show an extended response to suxamethonium; the two patients described by Evans and his colleagues

(1952) may have been in this group. In a Canadian population, Kalow and Staron (1957) have estimated that 96.4 per cent of persons have a dibucaine number over 70, 3.6 per cent have a dibucaine number between 40 and 70, and approximately 1 in 3,000 have a dibucaine number below 20—an incidence high enough to be of concern to anaesthetists.

Recently it has been possible to investigate seven cases of suxamethonium apnoea in children. Four of these were encountered by the author and three were referred from other hospitals. The ages of the children varied from 2 to 12 years and there were five girls and two boys in the series. The investigation was also extended to include the parents and siblings of the affected children. Pseudocholinesterase levels were measured by the photometric method using acetylcholine as substrate as described by Biggs, Carey and Morrison (1958) (normal range 100 to 180 Warburg units), and the dibucaine numbers by ultraviolet spectrophotometry as detailed by Kalow and Genest (1957).

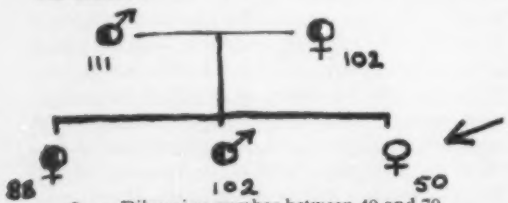
CASE REPORTS

CASE 1. Lyndsay McL., aged 10 years; weight 3 st. 8 lb. (22 kg).

Operation. Cystoscopy for urinary infection.

Premedication. Trimeprazine 30 mg, 4 hours pre-operatively; morphine 5 mg and atropine 0.6 mg, 1 hour pre-operatively.

Anaesthesia was induced with thiopentone sodium 75 mg intravenously followed by suxamethonium chloride 25 mg. An endotracheal tube was passed and controlled ventilation instituted using nitrous oxide and oxygen, 5 and 3 l./min respectively and Ayre's T-piece with a double-ended bag as described by Rees (1959). Apnoea lasted 45 minutes. Faradic stimulation of a motor nerve showed a non-depolarizing block and with the return of spontaneous respiration edrophonium 3 mg was given intravenously. Marked improvement in the depth of respiration occurred and following atropine 0.6 mg and neostigmine 1.5 mg adequate respiration was present and recovery from anaesthesia was prompt; no residual myoneural block was detected.



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

FIG. 3

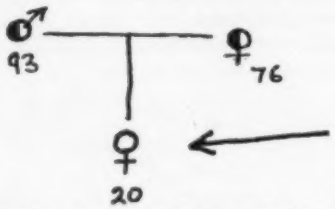
Comment. In figure 3 the pseudocholinesterase estimations and the dibucaine numbers in this family have been plotted. Although the patient has a low pseudocholinesterase level, the father, mother, brother, and sister are within the normal range. The father, mother, brother, and sister all have dibucaine numbers which show them to be of the intermediate type, whereas the patient's dibucaine number was 5.

CASE 2. Christine R., aged 2 years; weight 19 lb. (8.6 kg).

Operation. Bilateral release of trigger thumbs.

Premedication. Atropine 0.45 mg given 1 hour pre-operatively.

Anaesthesia was induced with thiopentone sodium 40 mg followed by suxamethonium chloride 25 mg. Intubation was performed and controlled ventilation instituted using nitrous oxide and oxygen, 5 and 3 l./min respectively with an Ayre's T-piece and double-ended bag. Apnoea persisted for 60 minutes and resumption of spontaneous respiration was associated with a marked tracheal tug; faradic stimulation of a motor nerve showed a typical non-depolarizing block. Edrophonium 1.5 mg produced an improvement in the depth of respiration, and following atropine 0.3 mg and neostigmine 0.8 mg intravenously, the patient made a rapid and uneventful recovery.



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

FIG. 4

Comment. The results of the pseudocholinesterase estimations and dibucaine numbers in this family are shown in figure 4. One of the parent's and child's pseudocholinesterase levels are reduced below normal. The dibucaine numbers of the parents were between 40 and 70 but the patient's dibucaine number was only 17.

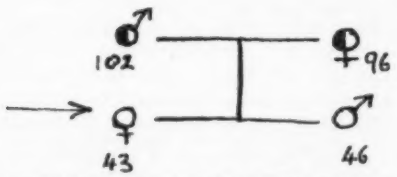
CASE 3. Pauline Ct., aged 10 years; weight 3 st. 8 lb. (22 kg).

Operation. Skin graft to foot.

Premedication. Trimeprazine 30 mg, 4 hours pre-operatively; atropine 0.6 mg, 1 hour pre-operatively.

Induction of anaesthesia was accomplished with thiopentone sodium 85 mg followed by suxamethonium chloride 50 mg intravenously. The patient was intubated and controlled ventilation was started with nitrous oxide and oxygen using an Ayre's T-piece and double-ended bag. Apnoea continued for 105 minutes and at this time a non-depolarizing block was demonstrated on faradic stimulation of a motor nerve; 30 minutes later there was a marked tracheal tug. The myoneural block was reversed by atropine 0.45 mg

followed by neostigmine 1.5 mg. The patient awoke and removed the endotracheal tube. Over the next 10 minutes spontaneous respiration gradually became inadequate and the tracheal tug reappeared. The patient was re-intubated with ease and controlled ventilation was restarted with nitrous oxide and oxygen. Sixty minutes later spontaneous respiration was judged to be adequate and on discontinuing the nitrous oxide, the patient awoke. The subsequent course was uneventful.



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

FIG. 5

Comment. This case demonstrates the importance of keeping the patient under close observation during recovery from a prolonged apnoea and also the transient effect that neostigmine may have if given too early in the recovery from this type of neuromuscular block. In figure 5 it can be seen that although the father's and mother's pseudocholinesterase is normal, the brother's and patient's pseudocholinesterase levels are below normal. Both the parents have dibucaine numbers between 50 and 70, and both the children have dibucaine numbers below 20. The brother has never had an anaesthetic, and it can be predicted that if he were given suxamethonium 1.6 mg/kg, a prolonged neuromuscular block would develop.

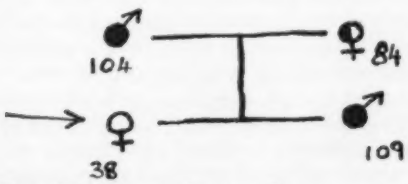
CASE 4. Lynn Cr., aged 2½ years; weight 28 lb. (12.7 kg).

Operation. Release of trigger thumb.

Premedication. Trimeprazine 30 mg 4 hours pre-operatively; morphine 3 mg and atropine 0.6 mg, 1 hour pre-operatively.

Anaesthesia was induced using thiopentone sodium 50 mg which was followed by suxamethonium chloride 50 mg. An endotracheal tube was passed and ventilation controlled with nitrous oxide and oxygen, using an Ayre's T-piece and double-ended bag. Apnoea was present for 90 minutes, and on resumption of spontaneous respiration a non-depolarizing block was demonstrated on faradic stimulation of a motor nerve. The rectal temperature was 98.8°F (37.1°C). Edrophonium 3 mg was given 15 minutes after the return of spontaneous respiration and following a marked improvement in muscle tone, neostigmine 1 mg, preceded by atropine 0.3 mg intravenously restored adequate respiration. The patient promptly awoke when the nitrous oxide was turned off.

Comment. The pseudocholinesterase estimations show that although the patient's and mother's levels are subnormal, those of the rest of the family are within the normal range (fig. 6). The dibucaine numbers of the father and brother show them to have typical pseudocholinesterase, whilst the mother's dibucaine number of 61 is in the intermediate range, yet the patient's number is 8.7, showing her to possess only atypical pseudocholinesterase. The significance of this familial pattern will be discussed later.



● = Dibucaine number over 70.
◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

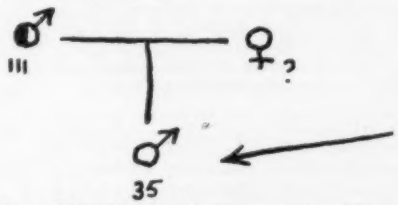
FIG. 6

CASE 5. Thomas M., aged 6 years; weight 3 st. 8lb. (22 kg).

Operation. Reduction of compound fracture of radius and ulna.

Premedication. Atropine 0.6 mg, 45 min. pre-operatively.

Anaesthesia was induced by thiopentone sodium 100 mg intravenously followed by suxamethonium chloride 35 mg. The patient was intubated and a mixture of nitrous oxide 6 l./min with oxygen 3 l./min was used to control ventilation with an Ayre's T-piece and double-ended bag. Apnoea lasted 90 minutes. No drugs were given and respiration became adequate over the next 30 minutes.



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

FIG. 7

Comment. It was not possible to trace the mother of this child but the father's pseudocholinesterase level was normal, whereas the patient's was subnormal (fig. 7). The father had a dibucaine number of 43, whereas the patient's was zero.

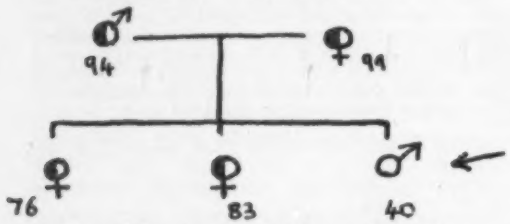
CASE 6. Stuart J., aged 5 years; weight not known.

Operation. Adenotonsillectomy.

Premedication. Papaveretum 8 mg and hyoscine 0.16 mg, 1 hour pre-operatively.

Anaesthesia was induced with intravenous thiopentone sodium 150 mg followed by suxamethonium chloride 40 mg. A nasotracheal tube was passed and ventilation was controlled with nitrous oxide 6 l./min

and oxygen 2 l./min together with minimal ether-halothane azeotropic mixture from a Rowbotham's bottle using a Magill attachment. The azeotropic mixture was discontinued after 10 minutes because spontaneous respiration did not reappear. Nalorphine 6 mg. edrophonium 5 mg and nikethamide 2 ml produced no effect. Ventilation was continued with oxygen only; 180 minutes later a tracheal tug appeared, associated with weak respiratory efforts. Two doses of edrophonium 5 mg produced a considerable improvement in the depth of respiration. Atropine 0.6 mg followed by neostigmine 1.25 mg were given and shortly after this the child recovered consciousness. Respiration remained adequate thereafter.



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

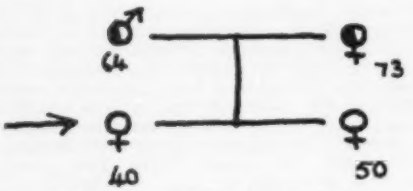
FIG. 8

Comment. The long duration of apnoea in this case may have been related to the dose of edrophonium that was given when it was realized that this child had a prolonged apnoea. It is interesting to note that the pseudocholinesterase levels of the parents are within normal limits whereas all the children's levels are subnormal (fig. 8). The patient had a dibucaine number of 3.4, and the rest of the family had dibucaine numbers in the intermediate range.

CASE 7. Janice T., aged 12 years; weight 6 st. (38 kg).
Operation. Adenotonsillectomy.
Premedication. Papaveretum 14 mg and hyoscine 0.3 mg, 1 hour pre-operatively.

Anaesthesia was induced with thiopentone sodium 200 mg followed by suxamethonium chloride 30 mg intravenously. A nasotracheal tube was passed and ventilation was controlled with nitrous oxide 6 l./min and oxygen 3 l./min with minimal ether-halothane azeotropic mixture from a Boyle's ether vaporizer using a Magill attachment; 5 minutes later the azeotropic mixture was discontinued, and ventilation was continued with nitrous oxide and oxygen only. Apnoea persisted for 45 minutes. Edrophonium 10 mg produced great improvement in the depth of respiration. Neostigmine 2.5 mg followed by atropine 1.2 mg resulted in adequate respiration, and the patient then rapidly regained consciousness when the nitrous oxide was discontinued.

Comment. In this case the dose of suxamethonium was only 5 mg/stone (0.9 mg/kg), which is half the usual initial dose, and the apnoea lasted for only 45 minutes. The pseudocholinesterase levels of the whole family are below normal limits. The dibucaine numbers of the parents are in the intermediate range, but both



◐ = Dibucaine number between 40 and 70.
○ = Dibucaine number below 20.
Numbers=Esterase activity in Warburg units.

FIG. 9

the children have dibucaine numbers of 20 or below. This case illustrates the importance of investigating not only the patient but also the family, so that adequate warning may be given if another member of the family is found to have a low dibucaine number, and hence will be sensitive to suxamethonium.

DISCUSSION

Can the thesis be accepted that prolonged apnoea following a single dose of suxamethonium is due to complete failure of the pseudocholinesterase to metabolize this drug in the concentration in which it is present in the plasma? Many cases of prolonged apnoea due to suxamethonium have been reported but in the majority of instances insufficient clinical and laboratory data are available to make it possible to determine whether these were really due to the prolonged action of suxamethonium. Few cases have been described in which the dibucaine numbers have been investigated (Kalow and Gunn, 1957; Harris et al., 1960). The small series reported here supports this thesis.

If, then, it be accepted that in certain individuals, their pseudocholinesterase is unable to destroy the injected suxamethonium, what type of neuromuscular block is produced? Since no electromyographic tests have been performed during a case of prolonged neuromuscular block of this kind, it is not possible to be dogmatic about which type of block is present. Certainly it is a most profound paralysis and it is tempting to think that, initially at any rate, a depolarizing block is present. Some evidence for this belief is to be found in the case described by Lehmann and Simmons (1958), in which apnoea of 90 minutes duration was readily reversed by an injection of concentrated pseudocholinesterase. On the other hand there is considerable evidence that in the later stages, a non-depolarizing block has been produced, in that

it is reversed by anticholinesterase drugs (Argent, Dinnick and Hobbiger, 1955; Ruddell, 1958; Abrams and Ginsberg, 1960). Certainly in four of the cases in the present series it was possible to demonstrate a typical non-depolarizing block on stimulation of a motor nerve as shown by tetanic fade and post-tetanic facilitation. In this respect these cases showed the same response as those patients who have received large doses of suxamethonium (Churchill-Davidson and Christie, 1959). Indeed it may be that these cases who show a prolonged block after a single dose are behaving in a manner identical with those normal persons who are given large doses of suxamethonium; in both conditions the level of suxamethonium at the motor endplate is maintained at a high concentration; in the first instance by failure of the pseudocholinesterase to destroy it, and in the second, by repeated infusions. So that just as in cases which are given large doses of this depolarizing drug, so in these cases of prolonged apnoea the neuromuscular block gradually changes from a depolarizing to a non-depolarizing type. There is probably no critical point at which the character of the block changes but the gradual development of a non-depolarizing type is unmasked by the subsidence of the original depolarizing type of block.

The gradual reduction in intensity of the depolarizing block is probably associated with a fall in the plasma concentration of suxamethonium. If enzymatic activity is not responsible for the destruction of this drug, some other mechanism must be involved. It is known that non-enzymatic hydrolysis of suxamethonium may occur in vitro and at high concentrations of substrate this can be very impressive. However, at a pH of 7.4 and at normal body temperature alkaline hydrolysis is very slow (Fraser, 1954). Whether this breakdown mechanism can be entirely responsible for the destruction of suxamethonium in the absence of active pseudocholinesterase, or whether some other method of elimination plays an important part, is still a matter for conjecture.

The changes that give rise to the development of a non-depolarizing block are still inadequately understood. Paton (1956) believes that there is in such cases an area around the motor endplate which is depolarized, the so-called desert area, and hence a large endplate potential is required to overcome this insensitive area. On the other hand, Thesleff (1956) believes that the endplate itself has changed its sensitivity to depolarizing drugs including the natural depolarizer. In both cases increasing the quantity of acetylcholine at the motor endplate by anticholinesterase drugs will overcome the block. Recent work with radio-active labelled depolarizing drugs would seem to suggest that the non-depolarizing neuromuscular block produced by these drugs, the so-called phase II block, is different from that produced by the true non-depolarizing group of drugs. In vitro d-tubocurarine uptake is not reduced and there is little release of radio-active labelled depolarizing drugs when large doses of d-tubocurarine are added to a nerve muscle preparation showing evidence of a phase II block, suggesting that different receptor sites are involved (Taylor, 1959). Furthermore, the rate of development of a phase II block is consistent with the slow uptake by the muscle fibres of the radio-active labelled depolarizer. The route of entry would seem to be via the motor endplate since, if the receptors here are blocked by d-tubocurarine, little uptake can be demonstrated. The presence of the depolarizing drugs within the muscle fibre around the motor endplate adds support to Paton's theory.

It has been shown in dogs (Stevenson, 1960) and in man (Paton, 1959) that suxamethonium causes an increase in the serum potassium level. It is tempting to think that a change in the electrolyte pattern inside the muscle cell may be responsible for the refractoriness to depolarization. A similar mechanism has also been held responsible in patients who have received an infusion of oxytocin, in whom the action of suxamethonium is changed from a depolarizing to a non-depolarizing block (Hodges et al., 1959). Indeed it has been recommended that an intravenous infusion of potassium chloride may be attempted when other therapeutic measures fail to terminate a suxamethonium induced apnoea (Foldes, Rendell-Baker and Birch, 1956).

There would seem to be no doubt that sensitivity to suxamethonium is a familial trait. Lehmann and Simmons (1958) reported the case of two brothers, both of whom were sensitive to suxamethonium, and Power (1958) described sensitivity in two sisters. As a result of investigations of cases of suxamethonium apnoea, Lehmann and Ryan (1956) found that there was a familial incidence of

low pseudocholinesterase levels. It was later postulated (Lehmann, Patson and Ryan, 1958) that, in healthy persons, three groups could be distinguished depending on their pseudocholinesterase values. The first group had levels over 90 Warburg units, and were classified as normal homozygotes; the second group, in which the pseudocholinesterase values lay between 36 and 60 units, were deemed to be heterozygotes; and the third group in whom the levels were below 20 units, were called abnormal homozygotes. There was, however, considerable overlap in the groups and in the 60–90 units range both normal homozygotes and heterozygotes could be found. Similarly, heterozygotes and abnormal homozygotes may have values in the range of 20–36 units.

The hereditary pattern of low pseudocholinesterase level bears a remarkable resemblance to the inheritance of atypical pseudocholinesterase described by Kalow and Staron (1957) who suggested that their findings can be explained on the basis that there exist two allelic autosomal genes without dominance. Thus if the letter A represents the gene for typical pseudocholinesterase and the letter B the gene for atypical a person with a high dibucaine number could be represented by the letters AA, those with a low dibucaine number by the letters BB, and the intermediate group by the letters AB. In order, therefore, that a child should have only atypical pseudocholinesterase (BB) it is necessary either that both parents are of the intermediate type (AB) or that one of them is homozygous for atypical pseudocholinesterase (BB) and the other heterozygote (AB).

It has recently been demonstrated very clearly by Harris and his co-workers that these two hereditary patterns are in fact synonymous (Harris et al., 1960). They were able to show in eleven cases of suxamethonium sensitivity that all had low dibucaine numbers and also low pseudocholinesterase levels. Furthermore, there was a correlation between the three ranges of dibucaine numbers as described by Kalow and Genest (1957) and the three levels of pseudocholinesterase suggested by Lehmann, Patson and Ryan (1958). It was postulated that the dibucaine number and esterase activity are characteristics of the same enzyme. These findings conveniently reconcile the two apparently divergent observations of Kalow and Genest and Lehmann, Patson and Ryan.

Unfortunately, the hereditary pattern is probably not as simple as has been suggested. In a family described by Kalow and Staron (1957) and in another investigated by Harris and his colleagues (1960) one of the parents of a child with a low dibucaine number had only typical pseudocholinesterase and therefore, according to the present thesis, could not have a child with only atypical pseudocholinesterase. It has been suggested (Harris et al., 1960) that this anomaly could be explained by the presence of an allele which leads to a low esterase activity and could be regarded as virtually inactive. Such an allele in combination with a typical allele would give rise to a high dibucaine number but a low esterase activity, whilst in combination with an atypical allele would result in a low dibucaine number and an esterase activity even lower than is to be expected. In the family Cr. (case 4) in this series, where the father had a high dibucaine number, this explanation would not seem to be adequate. Apart from this discrepacy, there are the details which are not adequately explained by the present concept of inheritance, and almost certainly minor modifications will have to be made as more information becomes available.

An interesting point is raised by the findings of Harris and his colleagues (1960) and of the present series. The combined total of eighteen cases, who are known to be suxamethonium sensitive and have low dibucaine numbers, also have low pseudocholinesterase levels. One is tempted to wonder whether those cases who had a suxamethonium apnoea and at the same time a normal pseudocholinesterase level were genuinely sensitive to suxamethonium. This anomaly may be explained by the knowledge that enzyme activity varies according to the substrate used. When esterase activity is estimated by the method of Smith and his colleagues (1959) using phenylbenzoate each of the patients in this series known to be suxamethonium sensitive was shown to have a much higher value than was the case when acetylcholine was the substrate (Biggs, Carey and Morrison, 1958). Different laboratory techniques for measuring esterase activity may account for the failure of this series to conform to the pattern described by Lehmann, Patson and Ryan (1958), in that there is a wider scatter of pseudocholinesterase levels in the heterozygote and abnormal homozygote groups.

TREATMENT

The first aim, as in any case of prolonged apnoea, is the maintenance of adequate ventilation. Though there are reports in the literature that, despite oxygen alone being administered, the patient was amnesic for the period of the apnoea, it is wiser to continue ventilation with a mixture of equal volumes of nitrous oxide and oxygen. Using such concentrations, it is possible to guard against the return of consciousness and at the same time provide adequate oxygenation. Bourne (1953) points out that when paralysis is complete there is no sign which indicates that consciousness has returned, and similarly advocates the use of nitrous oxide and oxygen for ventilation.

Faradic stimulation of a motor nerve will determine whether the block is of the non-depolarizing or depolarizing type. If there is evidence that the block it still of the depolarizing type, and a concentrated solution of pseudocholinesterase is available, it can be expected to terminate the apnoea. Anticholinesterases must not be given at this stage since they will potentiate the block. On the other hand, when a non-depolarizing type of block can be demonstrated, anticholinesterase drugs can be expected to accelerate recovery, Edrophonium in an adult dose of 10 mg intravenously is a good therapeutic test before giving atropine 1.2 mg followed by neostigmine 5 mg. Even if no drugs are given, the condition is self-limiting and recovery can be confidently expected, although pulmonary ventilation may be needed for 3 or 4 hours. The duration of apnoea varies in direct proportion to the dose of suxamethonium given, so that it is wise never to administer more than 50 mg as an initial dose. Even after apparently complete reversal, the patient should be kept under close observation for the next 30 minutes to ensure that subsequent recovery is uneventful.

It may well be asked how this complication may be avoided. Certainly all patients who are known either to have a low dibucaine number or to have had a prolonged apnoea due to suxamethonium should be told of their sensitivity and warned to convey this information to the anaesthetist before further operation. Apart from the routine estimation of pseudocholinesterase levels and dibucaine numbers in patients likely to receive suxamethonium, there is no other method by which healthy suxamethonium sensitive patients may be distinguished. This approach is obviously impracticable. The only possible alternative is to use a test dose of suxamethonium prior to the main dose, as advocated by Bourne (1953) and described by Foldes (1959). The value of this procedure has already been reported by Power (1958), who showed that in a child in whom he suspected suxamethonium sensitivity, a dose of only 2 mg intravenously was followed by an apnoea of 3 minutes, whereas a similar dose in a normal child of the same age produced only slight depression of respiration.

It can be hoped, therefore, that as more of these cases of suxamethonium sensitivity are recognized and adequately investigated, not only will the pattern of inheritance of atypical pseudocholinesterase become clearer but also that, by a greater understanding of the mechanism involved, the incidence of prolonged apnoea due to suxamethonium will be reduced.

SUMMARY AND CONCLUSIONS

Suxamethonium apnoea is a term which must be reserved for those cases in whom a prolonged neuromuscular block due to suxamethonium can be demonstrated. Abnormal responses to suxamethonium may occur (*a*) following doses of the order of 1 to 1.5 g when a dual block may develop, (*b*) following a single injection when the return of muscle power is delayed for approximately 10 minutes, an extended response, and (*c*) following a single injection when a neuromuscular block lasting 1 to 2 hours develops, a prolonged response.

Recent work suggests that the prolonged response results from failure of suxamethonium hydrolysis due to the presence of an atypical form of pseudocholinesterase, which may be recognized by the inability of dibucaine to inhibit its activity in vitro. Using this test, three types of persons may be distinguished; those who have only typical, those who have a mixture of typical and atypical, and those who have only atypical pseudocholinesterase. A familial pattern can be found in these persons who inherit atypical pseudocholinesterase and it is estimated that 1 in 3,000 persons will have only atypical pseudocholinesterase.

Seven cases of suxamethonium apnoea are described and in all cases the familial pattern was investigated. In four cases a change from depolarizing to non-depolarizing type of neuromuscular block was demonstrated and it is highly probable

that this change occurs in all cases of suxamethonium apnoea. Although the apnoea is self-limiting, ventilation must be continued with a mixture of nitrous oxide and oxygen, but recovery from the non-depolarizing block can be accelerated by the use of neostigmine. The use of a test dose of suxamethonium may abolish this unnecessary and inconvenient complication of the use of suxamethonium.

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AWARENESS DURING SURGERY

A Study of its Incidence

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THERE have been sporadic reports of patients who, although apparently anaesthetized adequately, felt pain or described conversations and incidents which undoubtedly occurred during operation (Winterbottom, 1950; Mushin, 1951; Graff and Phillips, 1959; Alment, 1959). Attention has been drawn to the risk that the patient might be awake during operation, when anaesthetic techniques involving large doses of relaxants are used (Mushin, 1951; Editorial, 1959; Parkhouse, 1960). However, no attempt seems to have been made to assess the incidence of this phenomenon in an environment of expert modern anaesthesia and the purpose of this paper is to describe such a study.

METHOD

During two periods, each of about five weeks, post-operative visits were made to all patients who had received general anaesthesia in any one of four operating theatres, three of which were used for general and emergency surgery, and one for gynaecological surgery and neurosurgery. Twenty anaesthetists, ranging in status from consultant to senior house officer, gave the anaesthetics. Children under 16 years were excluded because of the uncertainty of accurate communication; excluded also were patients undergoing intracranial surgery because of the frequency of unconsciousness and semiconsciousness in the pre- and postoperative periods.

The postanaesthetic enquiry was made to seem part of the usual routine visit. Questions about the last pre-operative and first postoperative recollection led up to the main question: "Did you dream during your operation?" Great care was taken that neither patients nor nursing staff realized the purport of the investigation. For this and other obvious reasons, no patient was asked directly whether he remembered his operation, although one or two patients at once described some recollection as a reality rather than a dream. The small number of patients who had "dreamt" were all listened to with equal interest but only those "dreams" which seemed to have any possible relationship with surgical or anaesthetic procedures were recorded in detail. In these cases careful histories and details of anaesthesia, including time and dosage of premedication, and any observation made by the anaesthetist concerned were noted. The collection of these data was simplified by the routine use of anaesthetic records in this unit. The patient's dream was then compared with the events in the operating theatre to see if there was any possible connection between the two.

RESULTS

The total number of patients involved was 700, of whom 656 form the series to be described. Satisfactory answers to the enquiry were not obtained from the other 44 patients for the reasons set out in table I.

TABLE I

Minor cases (mainly cystoscopies) who were discharged from hospital on the day of operation or before the author's visit next day	30
Patients who were too ill to question, senile or imbecile	11
Patients speaking only Eastern European languages	3
Total	44

The details of the 656 remaining are listed in table II. Only 9 patients had dreams which appeared to have any possible connection with events in the theatre, and only 8 of these fall within the scope of the study as the story of the ninth patient was rejected. The details of these cases are reported below.

*At present at the Department of Anaesthetics, St. Thomas's Hospital, London, S.E.1.

TABLE II

Results of postoperative interview.

Patients who neither dreamed nor remembered part of their operation	628
Patients who had dreams unrelated to their operation	19
Patients who had a dream or experience apparently related to operation	8
Patients who had a dream related to operation, but whose story was rejected	1
Total	656

CASE REPORTS

CASE 1. An obese 36-year-old woman.

Operation. Repair of supra-umbilical hernia.

Anaesthesia. Papaveretum 20 mg, hyoscine 0.4 mg given 1 hour pre-operatively. Thiopentone 500 mg, gallamine 180 mg, pethidine 15 mg. Nitrous oxide 3 l./min, oxygen 1.5 l./min. Intermittent positive pressure respiration. Duration 1 hour. Patient began to breathe spontaneously during operation, pethidine and gallamine needed to regain control.

Patient's dream. She was struggling to remember the anaesthetist's name, she wanted to argue but could not "because there was something in my mouth, stopping me talking". "Someone was pushing something around in my stomach."

Discomfort: yes. Hearing: none. Vision: none.

Comment. The patient had an oral airway inserted for a minute or two after extubation but it was removed before she left the theatre. As she did not remember anything being put into or removed from her mouth, and as she was apparently prevented from talking by the object, it seems likely that it was the endotracheal tube. This patient was not upset by her experience.

Possible cause of anaesthetic resistance: (a) obesity; (b) occasional alcohol.

CASE 2. A 55-year-old woman with mild bronchitis.

Operation. Hemicolectomy for carcinoma of the caecum.

Anaesthesia. Promethazine 25 mg, pethidine 50 mg, atropine 0.6 mg given 1 hour pre-operatively.

Thiopentone 250 mg, gallamine 120+40 mg, nitrous oxide and oxygen. Intermittent positive pressure respiration. Duration 1½ hours. There was considerable bleeding during surgery, and intravenous plasma was started after some difficulty. The anaesthetic was purposely lightened at what was apparently the end of the operation but had to be deepened when the surgeon decided to turn the patient in order to insert a perineal drain.

Patient's story. The patient complained immediately she was back in the ward that she had felt during her operation abdominal pain "like red-hot needles". She had heard voices around her, including that of the surgeon who performed the operation. She also heard the loud noise of a machine and felt she was sliding up and down the table attached to it. She was unable to move or attract attention.

Discomfort: yes (pain). Hearing: yes. Vision: none.

Comment. The patient's story is a convincing one of mechanical artificial ventilation, about which she had no knowledge. The anaesthetist concerned felt that the experience described must have occurred at the end of the main procedure when the anaesthetic was known to be "light". As she did not remember being turned over, nor complain of the perineal incision, it seems more likely that the experience occurred earlier, possibly during skin suturing. The patient was angry and distressed.

No cause of resistance to anaesthetic drugs was apparent.

CASE 3. A wasted little old lady of 70 years.

Operation. Laparotomy and biopsy of carcinoma of head of the pancreas.

Anaesthesia. Morphine 10 mg, atropine 0.6 mg given 30 minutes before operation.

Thiopentone 150 mg, gallamine 80 mg with two increments of 20 mg, nitrous oxide 2.75 l./min and oxygen 1.25 l./min. Intermittent positive pressure respiration. Duration 1½ hours. There was no movement or loss of control of respiration during surgery. Additional gallamine was given for relaxation only.

Patient's story. She awoke in the theatre, with pain deep in the abdomen. The pain was associated with an irregular rapid clicking noise "like someone in a hurry". She thought at first that the clicking was due to cameras, but then decided she was being given "X-ray treatment". She also heard people talking about football.

Discomfort: yes (pain). Hearing: yes. Vision: none.

Comment. It was established that one particularly fast-working surgeon sewed up the posterior peritoneum and the deep layers of the anterior abdominal wall using a needle-holder with a ratchet. Another surgeon completed the closure using a different needle-holder. A forthcoming Cardiff-Springbok rugby match was discussed during the case.

This frail old lady became very distressed when an attempt was made to discover further details of her experience, and it was felt to be unjustifiable and unnecessary to continue to question her. In fact, when an attempt was made to re-open the subject a week later she denied any unpleasant experience: she had just had a bad dream.

This patient had had limited amounts of analgesic drugs before operation. Panadol (paracetamol) had been given for two weeks and in addition two doses of dihydrocodeine. There was no other obvious cause of anaesthetic resistance.

CASE 4. A rather obese 63-year-old woman who had been intermittently jaundiced.

Operation. Cholecystectomy for cholelithiasis.

Anaesthesia. Morphine 10 mg, atropine 0.6 mg given 1½ hours pre-operatively.

Thiopentone 300 mg, gallamine 100 mg with two increments of 40 mg. Nitrous oxide 4 l./min and oxygen 2 l./min. Intermittent positive pressure respiration. Duration: 1½ hours. During operation a considerable degree of hypertension was recorded 200/120 mm Hg), although the normal blood pressure was only 150/80 mm Hg.

Patient's story. She felt discomfort in the area of operation but could not move or attract attention. She knew there were people about her talking but could not remember the actual conversation.

Discomfort: yes. Hearing: yes. Vision: none.

Comment. There was no part of the patient's story

which could be checked. She was not at all upset by her experience. There was no obvious cause of anaesthetic resistance.

CASE 5. A rather excitable 48-year-old woman, with a blood pressure of 180/120 mm Hg.

Operation. Sigmoidoscopy, and cholecystectomy for cholecystitis.

Anaesthesia. Papaveretum 20 mg, hyoscine 0.4 mg given 1½ hours pre-operatively.

Thiopentone 300 mg, gallamine 200 mg. Nitrous oxide 3 l./min and oxygen 1½ l./min with 0.5 per cent halothane (Fluotec) V.O.C.* Intermittent positive pressure respiration. Duration: 1½ hours. The halothane was discontinued and washed out before the end of the operation. The patient moved a leg during closure of the abdomen and was told to lie still. Anaesthesia was deepened.

Patient's story. She was conscious of a "gnawing" sensation under the right ribs. She wanted to move, but felt compelled to be still. After a time she felt able to move a little "because the pain was getting rather much" and moved her left foot. She heard a "voice from above" telling her to lie still.

Discomfort: yes (pain). Hearing: yes. Vision: none.

Comment. This patient seemed excited by her experience. She later spontaneously wrote as follows: "Increasingly I believe that there is a level during anaesthesia where one feels and knows everything that is going on but there is no distress. . . . The memory I have is one of exultation and complete confidence. This has occurred each time I have had an anaesthetic."

No cause was found for any resistance to anaesthetic agents.

CASE 6. A healthy 38-year-old female.

Operation. Hysterectomy for fibromyomata.

Anaesthesia. Morphine 10 mg, hyoscine 0.4 mg.

Thiopentone 350 mg, gallamine 140 mg, Pethilorfan 100 mg, nitrous oxide and oxygen. Intermittent positive pressure respiration. Duration 1½ hours. During the early part of the case the ventilator appeared to be leaking. Even with high flow rates it would only give a positive pressure of 10 cm H_2O and manual intermittent positive pressure respiration was started because it was felt that the patient was being hypoventilated.

Patient's dream. The patient dreamt that the pages of a heavy book were being slowly turned over at regular intervals. There was a continuous noise which reached a crescendo during the effort of getting the page upright. The page then flopped over. She felt that she must struggle to wake up but could not.

Discomfort: none. Hearing: yes. Vision: none.

Comment. The possible relationship between this dream and a mechanical ventilator is mere conjecture. But, as the story was told, the time intervals and description of the background noise were very suggestive. The dream was not at all unpleasant to the patient.

No known cause of anaesthetic resistance was discovered.

CASE 7. A healthy 52-year-old woman.

Operation. Radical mastectomy for carcinoma of breast.

Anaesthesia. Morphine 10 mg, atropine 0.6 mg given 1 hour pre-operatively.

Thiopentone (dose not recorded), relaxant, nitrous oxide, oxygen and halothane. Intubation was "uneventful".

Patient's story. The worst part of the operation was the extremely unpleasant choking sensation when the "tube was put down my throat" after the injection. This happened before she became unconscious, she thought.

Comment. This patient had no knowledge of anaesthetic procedures.

CASE 8. A healthy 55-year-old woman.

Operation. Shea's operation for deafness.

Anaesthesia. Morphine 10 mg, atropine 0.6 mg.

Thiopentone (dose not recorded), suxamethonium 50 mg, nitrous oxide and oxygen with halothane.

Patient's dream. Elijah came and breathed into her mouth.

Comment. Possibly pre-intubation oxygenation.

REJECTED CASE.

The patient whose story was rejected was a girl of 26, who had had a partial thyroidectomy for a mildly toxic goitre. She claimed to have dreamt of her whole operation, describing the procedure in detail and at length, but often in the form of a question and always watchful to see the effect of her remarks upon the observer. There was no mention of pain, tracheal intubation, or of the noise of conversation or of surgical instruments. There were so many inconsistencies with what actually took place that this case was not felt to fall within the scope of the present study.

DISCUSSION

The purpose of this study was to discover whether any of a series of apparently adequately anaesthetized patients had experienced recovery of awareness during surgery. That this condition does occur has been demonstrated. As an assessment of its incidence, however, the study is obviously open to some criticisms, four of which will be considered.

There is very little proof that the experiences described by the patients really occurred during operation. Only case 3, who reported conversation and a noise similar to that of a needle-holder actually used, and case 5, who moved and overheard a remark subsequently made, tell of experiences which can be corroborated.

The cases are to a small extent selected. Some overnight-stay cases and some very ill patients were not questioned. Also, only certain types of surgical procedures were carried out in the few theatres concerned. Neither operative obstetrics nor chest surgery are included.

*V.O.C.=vaporizer out of circuit (Mushin and Galloon, 1960).

Although about twenty anaesthetists were concerned there were not wide differences in anaesthetic techniques. In fact in the majority of patients anaesthesia was induced with thiopentone and maintained either with nitrous oxide, oxygen and halothane if respiration was spontaneous, or with nitrous oxide and oxygen, muscle relaxant and intermittent positive pressure techniques when respiration was controlled.

The experiences described are not all clear cut, and might be described as a graded series. It could be argued that cases 6 and 8 at one end of the scale had no real "awareness", whereas case 3 gave an account that could hardly be doubted. Also, perhaps, cases 7 and 8 should be excluded because the events described probably occurred before consciousness was ever lost.

Incidence.

Although realizing the inadequacies of the study in calculating the incidence statistically, it was felt worth while to do so. As it seems self-evident that this condition is likely to be associated with the use of muscle relaxant drugs, the anaesthetic records of the whole series were collected and grouped according to the usage of these drugs (table III).

STATISTICAL ANALYSIS

(Dr. E. Lewis Faning)

Problem 1. What confidence can be placed in the percentages shown in table III?

For all groups combined, out of a sample of 656 patients, 8 had the characteristic of awareness during operation. This is 1.22 per cent, from which it can be calculated that one can say with 95 per cent degree of confidence (95 per cent confidence interval) that for a general population of anaesthetized patients, from which this sample is presumably drawn, the percentage would be between 0.4 and 2 per cent.

For group 2—2 cases out of a sample of 201 (1.0 per cent)—the confidence interval is from 0 to 2.3 per cent.

For group 4—6 cases out of a sample of 216 (2.78 per cent)—the confidence interval is from 0.6 to 5 per cent. In other words, 2.78 per cent of this group were aware, but because of sampling variation, we would be unwise to quote this as more accurate than somewhere between 0.6 and 5 per cent. But this range of accuracy has a 95 to 5 chance (95 per cent) of being correct. (Similar for the two previous paragraphs.)

Problem 2. Are the differences between the proportions who were aware in the four groups significant, i.e. are these differences greater than would be expected to arise just by chance?

Clearly since no cases arose either in group 1 or group 3, no test of significance can be applied. So I have combined these groups and get:

Group		Percentage "aware"
1 and 3	No relaxant, or small doses over a long period	0
2	Relaxants for short time (early in operation)	1.0
4	Relaxants in large doses	2.78
	All groups	1.22

Statistical tests suggest that the differences between the three sub-divisions is significant, but due to smallness of numbers, some technical difficulties prevent one from being dogmatic.

But if we compare group 4 against the rest (i.e. 2.78 per cent against 0.46 per cent) this difference is unlikely to be due merely to chance ($\chi^2=4.7$; $n'=1$; $0.05>P>0.02$).

TABLE III

Occurrence of awareness during surgery according to the usage of muscle relaxants.

	Total	Patients subsequently found to have been "aware"	
		No.	Per cent
Patients given no muscle relaxants	181	Nil	Nil
Patients given short-acting relaxant for intubation only (rarely repeated)	201	2 (Cases 7 and 8)	1.0
Patients given small doses of long-acting relaxants. Respiration spontaneous	58	Nil	Nil
Patients given large doses of long-acting relaxants. Respiration controlled	216	6	2.78
Totals	656	8	1.22
*Excluding cases 7 and 8	656	6	0.91

*These cases were possibly describing events occurring before loss of consciousness.

If we compare group 2 with group 4 (1.0 per cent with 2.78 per cent) the difference is not significant. Nor is the difference between group 2 and groups 1 and 3 combined (1 per cent and 0 per cent).

But group 4 is significantly different from groups 1 and 3 combined ($\chi^2=4.76$; $P<0.05$).

To sum up, it seems that group 4 with large doses of relaxants gives somewhere between 0.6 and 5 per cent who were aware. This sample percentage (2.78 per cent) is significantly higher than that given either by groups 1 and 3 together, or groups 1, 2 and 3 together.

AETIOLOGY

The possible causes for this condition will be considered, with reference to the cases described where this is possible.

Reduction in percentage of nitrous oxide in the inspired mixture.

The percentage of nitrous oxide which is considered optimal in the inspired gas mixture varies with the anaesthetist but is usually between 60 and 80 per cent. Where known in the cases described it was about 70 to 75 per cent. Experience with outpatient nitrous oxide anaesthesia, confirmed by Bourne's experiments (Bourne, 1960), suggests that even 80 per cent nitrous oxide in oxygen is inadequate alone to produce loss of awareness in all individuals. But using the technique under discussion, even if there is no premedication or other pharmacological supplementation, the use of muscle relaxants and hyperventilation is an integral part of the technique. The percentage of nitrous oxide necessary in these circumstances is virtually unknown. Unfortunately Rosen's interesting study (Rosen, 1959) of 58 patients' recollections of auditory stimuli was carried out on postoperative cases, an unknown number of whom were still being artificially ventilated. One patient, however, is described who recollected noises played to her from a tape recorder during the operation of cholecystectomy, while nitrous oxide 71 to 73 per cent was being given.

However, while realizing that the generally accepted nitrous oxide percentage in the inspired gas mixture may not always be adequate, there are occasions when this percentage is purposely or inadvertently reduced. For example, many anaesthetists give a rather higher percentage of oxygen to cardiac and very ill patients. The obvious and commonest cause of inadvertent reduction in nitrous oxide percentage is a nitrous oxide cylinder which runs out unnoticed. Although there is no evidence of this having happened in any of the cases described here, it is a sufficiently common occurrence that an anaesthetist is likely to forget during which of the cases on an operating list the nitrous oxide cylinders were changed, and whether or not the bobbin on the flowmeter was noticed to be falling before it reached zero. It is pertinent to add here that in the four theatres used during this study there was not a piped nitrous oxide supply, cylinders being used. Also, mechanical ventilation was commonly employed, so that the feel of a reservoir bag which was failing to fill as rapidly as before would not be appreciated.

Another possible cause of inadvertent reduction of nitrous oxide percentage is the dilution of the inspired mixture with air or oxygen. For example, with some mechanical ventilators air may be drawn in if the fresh gas flowrate is insufficient, or through leaks in the system, especially if there is a negative pressure phase (Cole, 1955). Oxygen bypass taps can be left on unwittingly. Waters has measured a leak of 1.5 l./min on a Boyle's apparatus with a faulty oxygen bypass tap (Waters, 1960, personal communication).

Resistance to nitrous oxide anaesthesia.

Bourne (1960), in a study of the potency of nitrous oxide used as a sole anaesthetic, asked his patients about their consumption of alcohol and other central nervous system depressants. He concluded that the influence of acquired tolerance to central nervous system depressants was of paramount importance. "Acquired tolerance appeared to be not simply the main but the only factor influencing a patient's response to nitrous oxide after the induction period." In this study, therefore, the eight patients were asked about their alcohol intake and drug habits. None admitted more than an occasional drink except case 1, who had a "bitter or cider when playing skittles", apparently a few nights a week. However, patient 3 had been taking the mild analgesic paracetamol for 2 to 4 weeks and also dihydrocodeine for 2 days.

Inadequate supplementation of nitrous oxide anaesthesia.

It is difficult to discuss this factor as it has not

been established that any supplementation is needed for techniques using nitrous oxide and oxygen and controlled respiration. For example, many anaesthetists use no hypnotic or narcotic drugs in premedication or thiopentone for induction of anaesthesia in their cardiac cases. All the patients in this study had both narcotic premedication and induction of anaesthesia with thiopentone. Cases 1 and 6 received intravenous pethidine during surgery and case 5 received halothane 0.5 per cent although the incident recollected by the patient occurred after the halothane had been washed out. Unfortunately, the indications for supplementation of nitrous oxide are not defined but it may be—as pointed out by Siker (1956)—that there is a great need for a means by which gas can be potentiated safely.

Hypoventilation.

Gray and his colleagues pointed out the importance of hyperventilation in techniques employing nitrous oxide and oxygen, intermittent positive pressure respiration and muscle relaxants (Gray and Rees, 1952; Geddes and Gray, 1959). The hypnotic effect of low Pco_2 levels has been established (Clutton-Brock, 1957). Failure to hyperventilate seems a likely explanation in case 6, where trouble occurred with the ventilator. Cases 2 and 5 both remembered events occurring towards the end of the operation at a time when the effects of relaxants are often wearing off, and when the Pco_2 level is being allowed to return to normal prior to the re-establishment of spontaneous respiration.

Inadvertent hypoventilation can occur quite easily. Particularly when a respirator is used, there may be a considerable discrepancy between the volume recorded by the machine and that actually reaching the patient's lungs—a fact not always appreciated.

The anti-analgesic action of thiopentone.

All the patients in this series received this drug, It cannot be excluded that, particularly in the early operative period, the pain-relieving effect of analgesic drugs was reduced by the simultaneous action of small amounts of thiopentone in the blood (Clutton-Brock, 1960; Dundee, 1960), although the hypnotic effect of the latter was no longer effective.

CONCLUSION

There seems little doubt that it is possible for patients to be in a state of awareness during operations performed under techniques employing nitrous oxide and oxygen with muscle relaxants. Fortunately it appears that the incidence is low. In this series of 656 patients, only 6 of 216 anaesthetized using this technique reported any experience which could possibly be related to anaesthesia. Of these, only one or two remembered events which clearly did occur. Thus the statement that 0.6 to 5 per cent of patients anaesthetized in this way are likely to be "aware" is more likely to be an exaggeration than an understatement because all these 6 cases were included in the statistical evaluation. Also although in this series about 1 per cent of all anaesthetized patients were found to be "aware" this figure is not of much importance because it has been shown to depend principally on the proportion of cases anaesthetized by one particular technique, which obviously varies in different practices.

The difficulty of recognizing this occurrence has not been mentioned. All that can be said from this small series is that the patients were all women and that more often than not the events recalled took place at the end of operation. Hearing seems to be the first sense to return and vision the last. There may be no obvious physical signs. Prophylaxis must depend on the use of adequate nitrous oxide concentrations, possibly with supplementation and hyperventilation.

Is the possibility of awareness during surgery important? In this series of 656 patients only one (case 2) complained immediately after return to the ward, but there seems no doubt of the pain experienced by case 3. The other patients, particularly case 5, did not seem distressed. Parkhouse (1960) commented on the dispassionate manner in which the experience of awareness during surgery is often recalled, and felt that this is not due to repression of a terrifying experience into the subconscious, as this would be expected to produce a high incidence of anxiety states and fear of subsequent operations which is not apparent in clinical practice. There is evidence from this study that this is not always the case. It is possible that case 3 changed her story because the experience had been repressed. Also there were two patients in this series who claimed to have felt

part of a previous surgical procedure. They made their justifiable anxiety quite obvious. It is unfortunate that this anxiety is very easily communicated to other patients in the ward, possibly more so than to the medical staff.

It can be concluded, therefore, that every possible effort must be made to ensure complete and continuous unconsciousness during general anaesthesia, not only because of the moral obligation of the anaesthetist to provide freedom from physical and mental suffering which might otherwise occur in a very small percentage of cases, but also because of the disproportionate anxiety which knowledge of such a case may induce in other patients.

SUMMARY

A follow-up study of 656 general surgical, gynaecological and neurosurgical patients is reported in which enquiry was made into the patient's recollection of the operative period and dreams during anaesthesia. Eight patients either remembered some part of the procedure or had a dream suggestive of a partial return to consciousness. Case histories are tabulated. Excluding two cases, because they might have been describing events occurring prior to the onset of unconsciousness, all the remaining six were in the group of patients whose anaesthesia was maintained with nitrous oxide and oxygen, relaxants, and intermittent positive pressure respiration.

The aetiology of the condition is considered with reference to these cases. It is felt that inadequate nitrous oxide percentage and lack of hyperventilation are the most likely causes. A brief assessment of the importance of this condition is made.

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EARLY USE OF THE CARBON DIOXIDE ABSORPTION METHOD IN ANAESTHETIC PRACTICE*

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THE chemical absorption method for carbon dioxide control has gained widespread use in the respiratory equipment commonly used in anaesthetic practice, metabolism testing, chemical warfare defence, mine rescue work, diving and in high altitude operations. The researches of Hales, Black, and Lavoisier provided the foundation for the chemical absorption of carbon dioxide in respiratory equipment. It is of interest to review how this method of carbon dioxide control was introduced into anaesthetic practice.

BRIEF BIOGRAPHY OF ALFRED COLEMAN (1, 2, 3)

Alfred Coleman (1828–1902), a dental surgeon of London, England, employed the carbon dioxide absorption method during nitrous oxide anaesthesia in 1868. Coleman was born at Wandsworth in December 1828 of a Quaker family. He was apprenticed in 1857 and later set up practice at 3 Finsbury Square, near St. Bartholomew's Hospital, where he obtained instruction in anatomy. Coleman passed M.R.C.S. and L.D.S. in 1860 and L.R.C.P. in 1866. In 1868 he was the first dentist to pass the F.R.C.S. by examination.

Coleman was one of the original members of the Odontological Society, serving in all its honorary offices including that of president in 1879. In 1866 he was appointed lecturer in dental surgery at St. Bartholomew's Hospital in succession to Samuel John Tracy (4) and continued to lecture for fifteen years. During this period he was also president of the Abernethian Society (5). He was also dental surgeon at the Dental Hospital of London and lecturer at the London School of Dental Surgery at Soho Square. From 1880 to 1884 he served as an examiner for the L.D.S. examination of the R.C.S.

When Coleman joined Mr. Samuel Cartwright in practice (6), he moved from Finsbury Square to 32 Old Burlington Street. He became a member of the newly formed British Dental Association and when it was decided to purchase the *Monthly Review of Dental Surgery* as the organ of the association he served as an editor for two years. At this time Coleman moved from Old Burlington Street to Savile Row.

All through his long and productive life Coleman's chief interest lay in the scientific side of dentistry, especially in the new discoveries of anaesthetics. At the Dental Hospital of London, where he was associated with Clover, he administered anaesthetics every Thursday morning during his period of appointment and in 1881 he was able to report on 20,000 anaesthetics at that institution dating from 1868 (7). Coleman was always interested in chemistry and was awarded the prize in chemistry at St. Bartholomew's Hospital. He was helped a great deal by Sir Edward Frankland, F.R.S., lecturer in chemistry at St. Bartholomew's (8). He was the author of *Dental Surgery and Pathology*, which was published in 1882.

His health failed and he retired to New Zealand in 1884 for six years, returning to England in 1890, but he did not resume practice. He was made a Governor of St. Bartholomew's Hospital and Almoner in 1894 but declined a knighthood when it was offered to him. He died in Ealing in 1902.

COLEMAN'S METHOD OF CARBON DIOXIDE ABSORPTION

Thomas W. Evans, an American dentist practising in Paris, administered nitrous oxide gas as an anaesthetic to eleven patients for various operations of tooth extraction at the Dental Hospital, Soho Square, on Tuesday, March 31, 1868. Coleman was present at Evans' demonstration and by April 9 had arranged an apparatus, prepared the gas and administered it to five patients at the Dental Hospital (9a, b). At a meeting of the Odontological Society held on Monday, April 6, 1868, he discussed at some length the action of nitrous

* For reasons which will be apparent to the reader, the Harvard system of making reference to articles is not used in this paper.

oxide and its method of preparation (10a, b). On this same evening a committee was proposed to investigate the nature and uses of protoxide of nitrogen gas as an anaesthetic. The joint committee subsequently formed consisted of members from the Odontological Society and members appointed by the Board of Management of the Dental Hospital of London. Alfred Coleman was one of the members. The committee, known as the Nitrous Oxide Committee, made its first report on December 7, 1868, and its second report on November 4, 1872, followed by discussion on December 2, 1872. During the next few weeks Coleman demonstrated the administration of nitrous oxide on several occasions before a critical gathering for short operations at St. Bartholomew's Hospital and for teeth pulling at the Dental Hospital of London (11a, b; 12a, b, c, d). For the first trials with nitrous oxide he used an apparatus containing the gas in indiarubber bags to which was attached a tube-mouthpiece fitted with inspiratory and expiratory valves or an ordinary mask fitted with valves. At each inspiration the gas unmixed with atmospheric air was inhaled, expiration taking place through the other valve. Coleman had difficulty obtaining a correctly fitting mask and he soon substituted a facepiece "like that of Snow's". On June 11, 1868, he began to use the gas in a compressed form supplied by Mr. Barth.

Because of widespread interest in the physiological action of nitrous oxide the *British Medical Journal* for April 18, 1868, page 378, contains an annotation calling attention to the work of the physiologist, Ludimar Hermann of Berlin, published four years previously (13, 14). Hermann had shown that while nitrous oxide is very readily absorbed by the blood it suffers no change in the blood or in the body and is eliminated unchanged. Coleman grasped immediately the significance of this knowledge and responded in the following issue in the form of a letter (15) pointing out that if Hermann's researches were trustworthy, then the difficulty and expense of procuring and transporting nitrous oxide for anaesthetic purposes would prove to be minor considerations.

> . . . It is obviously evident that by a very simple mechanical and chemical arrangement, the same gas may be employed repeatedly. The products of expiration, now wasted, need only to be passed through a solution of caustic potash, and through pure water, or perhaps a weak acid, and returned to the receiver, whence the gas was inspired. The other products of respiration, not soluble in the above, are too small in quantity probably, to in any way affect the repeated breathing of the nitrous oxide over again. I need hardly say I am at once undertaking the proper steps for investigating so simple a suggestion as the above.

The editor of the *British Medical Journal*, in commenting on Coleman's letter, said "The difficulties of separating the expired gases from the products of respiration are greater than Mr. Coleman seems to suppose." However, Coleman proceeded with the development of his apparatus for absorbing carbon dioxide and on August 1, 1868, he reported that he had used the method in more than 100 cases with a saving of two-thirds to three-fourths of the quantity of nitrous oxide ordinarily consumed (16).

> . . . The agent I employ for removing the carbonic acid and aqueous vapour is quicklime recently or only partially slaked. The gas is admitted from a bag or receiver into a small indiarubber bag capable of holding about one gallon: from this it is inspired, but the expired gases pass over the lime and enter the bag again by another route. I will not say the gas so respired is as pure after it has passed over the lime as it was before it entered the lungs, but it is sufficiently so to bring a second patient who may breathe it into a state of anaesthesia in nearly the same period of time as the first, and that is no longer than when the gas is breathed only once. . . . In suggesting the plan of breathing the same gas over again, I did so under the belief that nitrous oxide gas is simply absorbed by the blood, and given off again without undergoing any change in composition as stated to be the case by Dr. Hermann whose experiments you recorded in your number of April 18th last. . . . An analysis of expired nitrous oxide made for me by Dr. Frankland, showed that the gas was exhaled undecomposed. . . .

In this same letter he discusses three patients who exhibited great excitement which he believes was caused by the presence of carbon dioxide. He had inhaled carbon dioxide admixed with air and it had produced excitement. "In looking carefully to the cause of these failures, I discovered upon examination that the lime employed had become exhausted, or rather, I should say, completely saturated with water and carbonic acid. . . ."

The first report of the Nitrous Oxide Committee hitherto referred to, was made at a meeting of the Odontological Society in the evening of December 7, 1868. Here Coleman briefly mentioned his method of rebreathing nitrous oxide and removing carbon dioxide. Several types of apparatus for administering nitrous oxide were exhibited. It is

not stated specifically that Coleman's apparatus was shown on that evening but the president of the society, in conducting the discussion, referred to the apparatus of Coleman and its "ingenious arrangements for economizing the consumption of gas in public practice". (17)

At the meeting of the Odontological Society on June 7, 1869 (18), the following report was made. For the sake of brevity only those parts of the report pertaining to the absorber are included.

> Mr. Coleman said, "Mr. Coxeter has sent for exhibition this evening an apparatus for the administration of nitrous oxide gas. . . . The bag is connected with a brass vessel which stands upon the pedestal, and into which, when about to be used, quicklime, slightly moistened, is introduced; a diaphragm in the centre of this vessel ensures the gas passing well over and through the lime; a tube from the lime apparatus has connected to it the face piece. . . .
>
> "In employing this apparatus the lime should first be placed after having been slightly moistened, in the brass vessel, and, this being securely closed, a small quantity of gas—a pint—should be forced from the bag through the vessel. . . . In trying this apparatus—the purifying portion of which Mr. Coxeter constructed according to my plans—at the Dental Hospital, we found that thirty-six gallons of gas were sufficient for the production of anaesthesia twenty-five times—in some of the cases anaesthesia was produced twice, and in one case three times, in the same patient, by simply adding about half a gallon of fresh gas to that the patient had previously breathed."

There is a description of the apparatus, called Mr. Coleman's economizing apparatus for re-inhaling nitrous oxide gas, contained in the *British Journal of Dental Sciences* for September 1869 and signed C.J.F., the initials of the editor, Charles James Fox (19). The description shows the same diagram as in figure 1 and states that "the apparatus is used by Mr. Coleman at the Dental Hospital of London every Thursday morning". The editor says:

> Although in the earlier days of the gas we were not inclined to look with favour upon apparatus which economized the gas by re-inhalation . . . we believe it has by this time been pretty conclusively shown that the gas when re-inhaled through this apparatus *can* be used not only with perfect safety but also with very fair anaesthetic results.

Coleman was dental surgeon to St. Bartholomew's Hospital and in the annual reports of that institution for 1869 he summarized his work on nitrous oxide administration during the preceding year. Here he gives a more elaborate account with illustrations of his apparatus (20).

> Before the gas had been presented in the compressed form it occurred to the writer that a vast economy in its use might be effected by a very simple means. Believing that nitrous oxide underwent no change when absorbed into the blood, and seeing this stated to be the fact by Dr. Hermann (13, 14), it occurred to him that the gas might be breathed over and over again, if means were provided for removing from it the carbonic acid which would be exhaled with it from the lungs. For this purpose, quick-lime slightly slackened with water was selected, over which the gas should pass to and from a small bag when respired. The result was that it was found to answer quite as well as when the gas was respired only once, and with a saving of from two-thirds to four-fifths of its quantity.

Figure 1 shows the main features of Coleman's absorber or "purifier" as he called it. Coleman states he obtained the drawings from Messrs. Coxeter who made the apparatus (21).

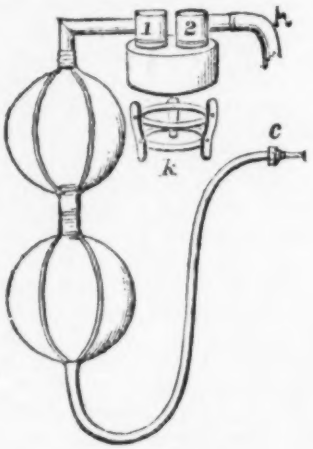

FIG. 1

Coleman's apparatus for carbon dioxide absorption. See text for description. (From *St. Bartholomew's Hospital Reports*, 1869.)

> Figure (1) represents at 1 and 2 the purifier into which the slackened lime is placed; with 1 is connected the double bag holding the gas, which communicates with (the source of gas) by the tube *c* and with 2 is connected the tube (*h*) leading to the facepiece; *k* is a tripod which supports the purifier . . . when the apparatus is in use.
>
> The mode of employing the apparatus is as follows: When the purifying plan is adapted, some small pieces of recently burned lime slightly moistened with water are put into the vessel at 1, 2 (fig. 1) which is then connected with the bag, here constructed as a double bag, and also with the tube *h* leading to the face piece, the bag being attached to the gas holder by the tube

c. . . . About a pint or two of gas should be pressed or sucked through the apparatus to remove air previously contained in it; the bag should then receive about a gallon and a half of gas from the gas holder. The patient being ready, if the operation be a dental one, the mouth should be propped open with a prop of wood or ebonite, secured to a string in case it should be swallowed, and the face or mouth piece applied. This should be furnished with an expiratory valve of thin indiarubber, to enable the patient to expire from it the first one or two expirations, which will be mixed with air (residual) previously contained in the lungs, after which a slide closing the valve is turned over it, and the patients now respires backwards and forwards over the lime into the bag until anaesthesia is effected, which occurs upon an average in sixty seconds from the time the gas is supplied to the patient (20).

Alfred Coleman reviews his use of the carbon dioxide absorption method in a paper delivered before the Odontological Society in 1881 (22). Here he states that from the earliest period of the introduction of nitrous oxide as an anaesthetic in England he was interested in devising means for its more economical administration. The cost of nitrous oxide was high at that time and Coleman stated that if it had not been employed at the Dental Hospital to a considerable extent upon economical methods it is questionable whether the charity could have borne so large an expense without demanding some fee from the patients or limiting the number of cases.

In discussing the various chemical agents which he used for carbon dioxide absorption, he says that whereas at first he used

. . . lumps of quicklime recently slaked with water. Other substances have since been employed for abstracting the carbonic acid, viz., milk of lime, solutions of caustic potash or soda: the gentlemen who suggested them evidently being unacquainted with the fact known to all practical chemists, viz., that of all substances we possess none so readily and so thoroughly abstract carbonic acid from other gases as does recently slaked lime, or rather lime in the process of slaking.

In this paper Coleman in discussing his reasons for discontinuing the carbon dioxide absorption method writes as follows:

In carrying out some experiments for the Committee appointed to investigate the merits of protoxide of nitrogen as an anaesthetic I found that as anaesthesia by its means approached, so the carbonic acid given off at the lungs greatly diminished, a fact subsequently confirmed by the experiments kindly made by Professor Frankland at my request for the same Committee. Indeed the amount became so small that it might be disregarded, and therefore I have long discarded the lime arrangement. Previously, however, Mr. Clover had introduced his useful contrivance of the supplemental bag, which allowed of a certain proportion of the gas being breathed over again. (23)

He does not state at what precise period of time he abandoned his method of carbon dioxide absorption. Since the cost of manufacture and distribution of nitrous oxide had been reduced in the intervening years from 1868 to 1881 it was not necessary to be so economical in its use, making it feasible to employ other methods of administration.

DISCUSSION

Barbara Duncum in her book on the history of inhalation anaesthesia (25) says that "Coleman's was the first clinical use of a carbon dioxide absorber in anaesthesia, although Snow had used a similar device while experimenting on himself with chloroform and ether; and Lavoisier and Seguin had used carbon dioxide absorbers to keep animals alive in closed vessels during experiments on respiration". Waters in his scholarly and informative history of the carbon dioxide absorption method in anaesthesia calls attention to the work of Coleman (24). Coleman was aware that carbon dioxide was absorbed by the alkali hydroxides and alkaline earth hydroxides since he was well versed in chemistry and such knowledge had long been known to chemists. John Snow made extensive researches on the toxic effects of carbon dioxide on small animals and on himself and had employed lime water for carbon dioxide absorptive purposes during experiments made in 1838, eight years before the introduction of ether anaesthesia. In reporting on his carbon dioxide experiments Snow mentions a plan suggested by Professor Thomas Graham on the possibility of absorbing carbon dioxide gas after the explosion of firedamp in coal mines by means of inhaling air through a cushion filled with a mixture of slaked lime and powdered sulphate of soda (26). There is reason to believe that Coleman might have been acquainted with the work of John Snow on carbon dioxide absorption contained in Part 15 of Snow's pamphlet, *On Narcotism by the Inhalation of Vapours* (1851), since Coleman quotes directly from Part 16 of that publication. Finally in assessing the influences upon Coleman, the association with Sir Edward Frankland made available to

Coleman information from one of the foremost British chemists of the nineteenth century.

The reasons for Coleman giving up his method of carbon dioxide removal have been referred to. Since economy was evidently an important motivation, the advent of lower cost nitrous oxide removed the impetus for perfection of the method and continued use.

The method was not taken up by his contemporary, Clover, who said (23): "Mr. Coleman has invented an ingenious apparatus for absorbing the carbonic acid of the expired gas by means of hydrate of lime. I have no reason to think that any harm results from the small amount of carbonic acid breathed in using my apparatus." Elsewhere Clover wrote (25, page 287): "I do not think enough gas is saved to pay for the trouble of purification and as yet I do not think his results are better than my own."

A contemporary, Rendle, surgical registrar at Guy's Hospital, also described his use of the gas (27).

> At first, I obtained the gas compressed in iron bottles from Mr. Barth, and gave it in the manner recommended by Mr. Coleman, which consists in causing the gas, when expired, to pass through a chamber of slaked lime. . . . This economizes the gas very much . . . but the apparatus required is rather complicated.

After obtaining an apparatus to produce the gas in large quantities, which he stored in a gasometer, he gave up the method of Coleman. He says: "Having now a store of gas at my command, economy was not studied, and it was given in the ordinary way from a large bag, with a mouthpiece having an inspiratory and expiratory valve."

Another contemporary referring to Coleman's method of purifying the gas of carbon dioxide wrote (28):

> I have always thought, and still think, that it will be damaging to the reputation of the gas in the eyes of the medical profession and of the general public, if the system of purifying and economizing it is adopted to the extent of permitting one patient to breathe that which has served the purpose of another. . . . How repulsive, then, must it not be to inhale a limited quantity of secondhand gas, deprived, it is true, of such carbonic acid gas as it may have acquired in its first use, but possibly impregnated with something deleterious.

SUMMARY

Alfred Coleman, a dental surgeon of London, England, used a carbon dioxide absorber in 1868 during nitrous oxide anaesthesia. Coleman was motivated to use the method because nitrous oxide at that time was difficult to manufacture and distribute, and therefore expensive. Since he knew that nitrous oxide underwent no chemical change when absorbed into the blood, it occurred to him that it could be breathed over and over again if a means were provided for removing from it the carbon dioxide which was exhaled with it from the lungs. Coleman preferred to use slaked lime in the absorber. He does not state when he gave up the method but in a paper published in 1881 he says he had long since abandoned the method.

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4. Thornton, J. L., Samuel John Tracy (1813–1901). The early use of anaesthetics at St. Bartholomew's Hospital, London. *Anaesthesia*, **7**, 72, April 1952.
5. The Abernethian Society, named after John Abernethy (1764–1831), is the student society of St. Bartholomew's Hospital Medical School for the reading and discussion of medical and surgical subjects.
6. Mr. Samuel Cartwright. There were two Samuel Cartwrights, father and son, prominent in the early development of the dental profession in Great Britain. The senior Cartwright, F.R.S., who left London in 1857, was first president of the Odontological Society formed in 1856. Samuel Cartwright junior, F.R.C.S., with other members of the Odontological Society played an important role in founding the Dental Hospital of London (Campbell, J. M. *From a Trade to a Profession: Byways in Dental History*. Glasgow: privately printed, 1958).

   John Snow mentions in his book, *On Chloroform and Other Anaesthetics: Their Action and Administration*, 1858, that he administered chloroform during extraction of teeth by Mr. Cartwright and Mr. Samuel Cartwright (page 314), and amylene for tooth extraction by Mr. Samuel Cartwright (page 387).

   For complete details and background of the development of the dental profession in England, see *History of the Reform Movement in the Dental Profession in Great Britain*, 1877, by A. Hill. Hill states that Coleman was active in this movement. See pages 44 and 346.
7. Coleman, A. Remarks on the administration of anaesthetics at the Dental Hospital of London from 1868 to the present time. *Transactions International Medical Congress*, **3**, 529, 1881.
8. Edward Frankland was born in Churchtown, Lancashire, in 1825. He was a pupil of Playfair, Bunsen, and Liebig, and occupied the chairs of chemistry in Owens College, Manchester (1851–57), St. Bartholomew's Hospital (1863), and the Royal Institution and the Royal School of Mines (1865). He died in 1899. For further details see McLeod, H., Obituary:

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AN ASSESSMENT OF THE MONO PORTABLE CARBON DIOXIDE TESTER

BY

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THE Mono portable carbon dioxide tester constitutes a simplification of the Van Slyke method of gas analysis (Van Slyke and Neil, 1924), by measurement of pressure at constant volume before and after absorption of one of the constituents of a gas mixture.

The apparatus has been investigated with a view to its possible usefulness in the medical field. Its principal characteristics are extreme simplicity and portability.

DESCRIPTION OF THE APPARATUS

The Mono carbon dioxide analyzer (fig. 1) consists of a hard polythene bottle partly filled with caustic potash covered with a thin layer of oil. The space in the bottle above the alkali is flushed out with the test gas by squeezing and releasing a rubber bulb, which sucks gas into the bottle. By turning a two-way tap the bottle is connected to a vacuum gauge and then shaken to break up the oil layer and bring about absorption of the carbon dioxide. The reduction in pressure is measured on the gauge, which is calibrated directly in percentage carbon dioxide.

SOURCES OF ERROR

(1) Changes in temperature due to warming of the bottle by the hand can cause an increase in pressure.

(2) Changes in vapour pressure may occur when the gas is in contact with the caustic potash. If a sample of dry gas is analyzed its pressure will be increased when it takes up water vapour from the alkali at the vapour pressure of the solution. When wet gas is analyzed its pressure may be decreased when it mixes with the alkali since caustic potash depresses vapour pressure and causes precipitation of water vapour in the sample.

(3) If the cap on the bottle or the rubber connec-

FIG. 1

The Mono portable carbon dioxide tester: the absorption vessel; the tap for collection of sample and connection of absorption vessel to vacuum gauge.

tions are badly fitting, leaks will occur, causing low results.

(4) The bottle can be distorted if much pressure is applied with the hand and this will cause changes in the indicated value.

(5) A layer of oil more than a millimetre thick is difficult to break up and complete absorption may not be achieved.

(6) Slight errors may occur from variable absorption of gases in connecting tubes and the vacuum gauge, which are not flushed with the test gas.

(7) Diluent gases in the sample may be soluble in the alkali or oil (Nunn, 1958).

METHODS

The volume of gas passed through the analyzer by squeezing the bulb was measured by connecting the end of the sampling tube to a calibrated spirometer. A carbon dioxide and oxygen mixture was analyzed many times using successively less gas in flushing out the bottle, to determine the minimum volume of gas required.

Four mixtures of carbon dioxide in oxygen, previously analyzed by a Haldane apparatus, were analyzed with this apparatus. Pure oxygen was also analyzed to check any zero error. The gases were sampled dry from the cylinder. Oxygen was also sampled from a spirometer where it had been allowed to become saturated with water vapour at ambient temperature.

The caustic potash solution was then replaced with alkaline pyrogallol to evaluate the instrument's ability to analyze oxygen.

Times for absorption to take place were noted throughout the tests. One hundred per cent nitrous oxide was sampled to observe any reduction of pressure due to physical solution of the gas in caustic potash. This was repeated with only oil in the bottle.

RESULTS

Fifteen squeezes of the rubber bulb (recommended by the manufacturer) correspond to 750 ml of gas. It was found that only ten squeezes of the bulb gave the same results as fifteen. Using less than ten, the results were not consistent. Ten squeezes correspond to 500 ml of gas.

With dry oxygen the analyzer gave readings varying from -0.3 per cent to -0.9 per cent according to the strength of the alkali used. With wet oxygen a zero reading was obtained. The minus reading with dry oxygen was probably due to the fact that the dry sampled gas took up water vapour from the alkali. The instrument can be adjusted to give correct readings with dry gas by offsetting the zero position of the needle on the gauge by the necessary amount, by means of the adjustment screw at the back.

Figure 2 shows the mean results of ten analyses on each of the four dry gas mixtures when the zero adjustment was offset. The range for the individual analyses is also shown. The standard deviation of the Mono analyses from the Haldane analyses was 0.2 per cent of the sampled volume.

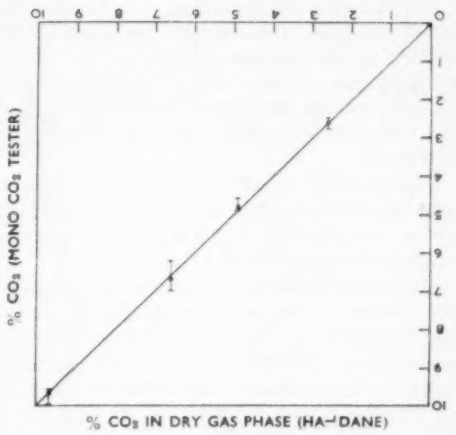

FIG. 2

Calibration curve for the Mono portable carbon dioxide tester compared with the Haldane apparatus, for mixtures of carbon dioxide and oxygen. The diagonal lines indicate the range of ten analyses of each mixture.

Eight analyses of air using the Mono apparatus with an alkaline pyrogallol oxygen absorbent gave a mean of 21 per cent oxygen (range 20.8 to 21.3 per cent).

It was found that the time required for the absorption of carbon dioxide from a sample of gas was 1 to 1½ minutes with vigorous shaking. Absorption of oxygen was complete in approximately 3 minutes. A thicker layer of oil increased the time and it might be difficult to be certain when absorption was complete.

A rapid reduction in pressure was observed when 100 per cent nitrous oxide was shaken with alkali and oil in the bottle, and to a lesser extent when oil alone was present.

CONCLUSIONS

The accuracy of this instrument is not comparable with the Haldane or Schölander but its simplicity and robustness render it suitable for use when a quick approximate analysis of carbon dioxide content of gas is required in hospital or laboratory.

The fact that the instrument can be used for oxygen analysis increases its possibilities. By substituting alkaline pyrogallol for caustic potash, the apparatus is ready without further modification and, though absorption is slightly longer, it still compares favourably with the Haldane or Schölander.

Unfortunately, as nitrous oxide is soluble in both the alkali and the oil, mixtures containing this or any other gas freely soluble in water or oil cannot be analyzed by this method.

The manipulation of the apparatus requires no skill whatsoever and an untrained person can be taught to use it in a matter of minutes. The few precautions to be observed are simple and easily learned: not to squeeze the bottle to distort it; not to warm it with the hand; to use only a very thin layer of oil (just sufficient to cover the alkali completely); and to offset the zero when analyzing dry gas. It is essential to prevent the alkali from reaching the connecting tubes, but if this happens they can be removed and washed.

One disadvantage of the apparatus is that at least 500 ml of sample are required for each analysis, but this is of little consequence when analyzing gases from cylinders, Douglas bags, oxygen tents or effluent from gas mixing devices (for example air entraining devices). It would also be suitable for the analysis of pooled end-tidal samples, but not single samples.

The present apparatus is a very simple application of the principle of measurement of gas pressure at constant volume. Clearly it could be modified to reduce the sample volume or increase the accuracy.

SUMMARY

A study of the Mono portable carbon dioxide tester has been made to assess its usefulness in the medical field.

The minimum sample required is 500 ml; no systematic error was found and the random error had a standard deviation of 0.2 per cent of sampled volume. Analysis for oxygen was possible by substitution of alkaline pyrogallol for caustic potash. Samples containing nitrous oxide or other gases freely soluble in water or lipids could not be handled.

The Mono tester was found to be extremely simple to use, requiring the minimum of skill and experience.

ACKNOWLEDGMENT

I should like to thank Dr. J. F. Nunn for his help and guidance in carrying out this study.

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ERRATA

The following corrections should be made to the payer on "A Simple Interpolation Method for the Estimation of Pco_2 in Whole Blood," by John S. Robinson and John E. Utting, in the July issue (*Brit. J. Anaesth.*, **33**, 327):

page 327, col. 2, line 3:
for 0.6 ml *read* 0.06 ml

page 328, col. 1, line 3:
for type C. 33 *read* type C.33B

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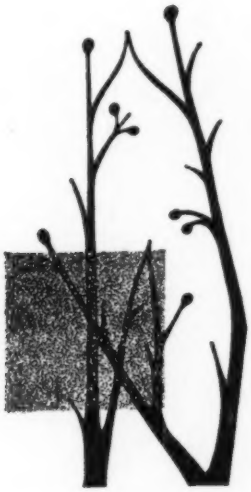

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